

CANCER

Rates and Risks

3rd Edition 1998

Office of Minority Health
Resource Center
PO Box 37337
Washington, DC 20013-7337



National Institutes of Health
National Cancer Institute

Editor in Chief: Angela Harras

Associate Editors: Brenda K. Edwards
William J. Blot
Lynn A. Gloeckler Ries

ACKNOWLEDGEMENTS

*The Editors gratefully acknowledge Drs. Susan Devesa, David Thomas,
and Max Myers for their valuable comments on the manuscript.*

Office of Minority Health
Resource Center
PO Box 37337
Washington, DC 20013-7337

CANCER

Rates and Risks

Cancer Statistics Branch
Division of Cancer Prevention and Control
National Cancer Institute

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

RATES

Lynn A. Gloeckler Ries, M.S.

Table of Contents

Background and Data Sources	9
Cancer Incidence in the United States (SEER)	
<i>10 Most Common Cancers by Sex Among Whites and Blacks, 1987–91</i>	<i>12</i>
<i>Changing Pattern for Major Cancers by Sex Among Whites and Blacks, 1973–91</i>	<i>14</i>
<i>Changing Patterns by Site Among All Races, Whites and Blacks, Males and Females . .</i>	<i>16</i>
<i>Age-specific Rates, All Sites by Age and Race</i>	<i>22</i>
<i>Time Trends (1973–91), All Sites by Age Group for All Races and Both Sexes</i>	<i>23</i>
International Range of Cancer Incidence	24
Cancer Survival Rates	
<i>Changes in the 5-Year Relative Survival Rates by Primary Cancer Site, All Races</i>	<i>28</i>
<i>Changes in the 5-Year Relative Survival Rates by Primary Cancer Site, Whites</i>	<i>29</i>
<i>Changes in the 5-Year Relative Survival Rates by Primary Cancer Site, Blacks</i>	<i>30</i>
Cancer Among Children Under Age 15	
<i>By Type of Cancer</i>	<i>31</i>
Cancer Mortality in the United States	
<i>10 Most Common Cancer Deaths by Sex, Whites and Blacks</i>	<i>32</i>
<i>Changing Patterns for Major Cancers in U.S. Males and Females, 1950–91</i>	<i>34</i>
<i>Changing Patterns for 11 Major Cancers in U.S. Males, 1950–91</i>	<i>35</i>
<i>Changing Patterns for 12 Major Cancers in U.S. Females, 1950–91</i>	<i>36</i>
<i>Changing Cancer Patterns, 1973–91 by Age Group for All Races and Both Sexes, All Sites Combined</i>	<i>37</i>
Cancer Death Rates Among 50 Countries	
<i>All Sites, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male and Female</i>	<i>38</i>
<i>Lung, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male and Female</i>	<i>40</i>
<i>Breast, 1986–88 Age-adjusted Death Rates per 100,000 Population, Female</i>	<i>42</i>
<i>Prostate, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male</i>	<i>44</i>
<i>Colon and Rectum, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male and Female</i>	<i>46</i>
<i>Stomach, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male and Female</i>	<i>48</i>
<i>Cervix Uteri and Other Uterus, 1986–88 Age-adjusted Death Rates per 100,000 Population, Female</i>	<i>50</i>
<i>Oral Cavity, 1986–88 Age-adjusted Death Rates per 100,000 Population, Male and Female</i>	<i>52</i>
References	54

Table of Contents

RISKS

RISK FACTORS

Air and Water Pollutants	56
<i>Kenneth P. Cantor, Ph.D.</i>	
Alcohol	61
<i>William J. Blot, Ph.D.</i>	
Anticancer Drugs	64
<i>Margaret A. Tucker, M.D.</i>	
Cigarette Smoking as a Cause of Cancer	67
<i>Donald R. Shopland</i>	
Diet and Cancer Risk	73
<i>Carolyn Clifford, Ph.D., Rachel Ballard-Barbash, M.D., Elaine Lanza, Ph.D., and Gladys Block, Ph.D.</i>	
Familial Factors	77
<i>Frederick P. Li, M.D., Mary Fraser, R.N., M.A.</i>	
Herpes Simplex Virus Type 2 and Human Papillomaviruses	80
<i>Allan Hildesheim, Ph.D.</i>	
Hormones	83
<i>Catherine Schairer, Ph.D.</i>	
Immunosuppressives and Other Drugs	87
<i>Robert N. Hoover, M.D.</i>	
Ionizing Radiation	90
<i>John D. Boice, Sc.D.</i>	
Occupation	94
<i>Aaron Blair, Ph.D.</i>	
Pesticides	99
<i>Aaron Blair, Ph.D.</i>	
Solar Radiation	103
<i>Joseph Scotto, M.S.</i>	
Viruses, Retroviruses, and Associated Malignancies	107
<i>William A. Blattner, M.D.</i>	

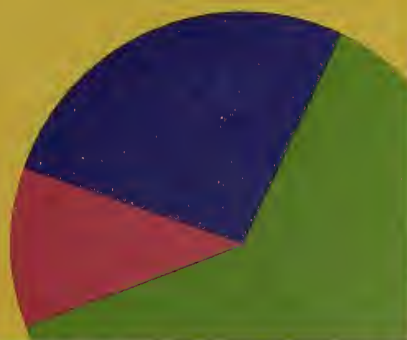
RISKS FOR MAJOR CANCERS

Biliary Tract	111
<i>Joseph McLaughlin, Ph.D.</i>	
Brain and Other Nervous System	114
<i>Terry L. Thomas, Ph.D., and Peter D. Inskip, Sc.D.</i>	
Breast	120
<i>Celia Byrne, Ph.D.</i>	

Table of Contents

Childhood	124
<i>Robert W. Miller, M.D.</i>	
Colon and Rectum	129
<i>Arthur G. Schatzkin, M.D., Dr.PH.</i>	
Esophagus	136
<i>Linda Morris Brown, M.P.H.</i>	
Hodgkin's Disease	140
<i>Paul H. Levine, M.D.</i>	
Kidney	145
<i>Joseph K. McLaughlin, Ph.D.</i>	
Leukemias	148
<i>Martha S. Linet, M.D., M.P.H.</i>	
Liver	155
<i>Adrian Di Bisceglie, M.D., F.A.C.S., and Edward Tabor, M.D.</i>	
Lung and Larynx	158
<i>Jay H. Lubin, Ph.D.</i>	
Melanoma of the Skin	163
<i>Mary C. Fraser, R.N., M.A., and Patricia Hartge, Sc.D.</i>	
Multiple Myeloma	167
<i>Linda M. Pottern, M.P.H., Ph.D.</i>	
Non-Hodgkin's Lymphoma	170
<i>Sheila Zahm, Ph.D.</i>	
Oral Cavity and Pharynx	175
<i>Gina L. Day, Ph.D.</i>	
Ovary	179
<i>Patricia Hartge, Sc.D.</i>	
Pancreas	182
<i>Roni Falk, M.S.</i>	
Prostate	185
<i>Richard B. Hayes, D.D.S., Ph.D.</i>	
Skin (Nonmelanoma)	188
<i>Joseph Scotto, M.S.</i>	
Stomach	191
<i>Robert Kneller, M.D.</i>	
Testis	194
<i>Linda Morris Brown, M.P.H.</i>	
Urinary Bladder	197
<i>Debra T. Silverman, Sc.D.</i>	
Uterine Cervix	200
<i>Louise A. Brinton, Ph.D.</i>	
Uterine Corpus (Endometrium)	203
<i>Louise A. Brinton, Ph.D.</i>	

RATES



The impact of cancer in a population is measured and described by looking at a combination of three elements: (1) the number of new cases per year per 100,000 persons (incidence rate), (2) the number of deaths per 100,000 persons per year (mortality rate), and (3) a determination of the proportion of patients alive at some point after their diagnosis of cancer (survival rate).

Background and Data Sources

Cancer occurs throughout the world, but the risk of cancer varies from region to region, suggesting geographic, environmental, and cultural implications.

Cancer incidence is monitored by population-based tumor registries around the world. Not all countries maintain population-based tumor registries and in many countries, including the United States, these registries monitor considerably less than the entire population. Incidence data from existing population-based registries from around the world are compiled by the International Agency for Research on Cancer (IARC), a part of the World Health Organization. The international incidence rates for the cancer sites presented in this section are taken from their publication, *Cancer Incidence in Five Continents (CI5)*, Volume VI (Parkin, 1992). To make meaningful comparisons among different countries, the rates are age-adjusted to the world standard population. The effect of age-adjustment is to eliminate differences in rates when the population of one country has a different age distribution from that of another country.

Many countries have vital statistics departments which keep track of cancer deaths for the entire country, providing a broad base for comparing cancer mortality rates across countries. For many specific cancers, and for all cancers combined, there are wide variations in death rates among different countries.

Background and Data Sources

The international mortality data are based on statistical analyses by the American Cancer Society of cancer mortality data provided by the World Health Organization (Boring, 1992). These rates are age-adjusted to the world standard (Parkin, 1992).

Death rates have been used to illustrate differences in cancer risk from one country to another. However, the diversity in mortality rates may be caused by a combination of contributing factors: different incidence rates, dissimilar distributions of prognostic factors such as stage, and differences in survival rates. For some sites such as lung cancer, where survival is poor, mortality is probably a good surrogate for incidence, but for cancer sites with good prognosis, mortality is not a good surrogate for incidence. When available, incidence rates, in addition to mortality rates, should be used to evaluate risk differences.

Today, in the United States, there are many statewide cancer registries and some regional registries based on groups of counties, many of which surround large metropolitan areas. Some of these population-based registries keep track of cancer incidence in their geographic areas only; others also collect follow-up information in order to calculate survival. In 1973, the National Cancer Institute (NCI) began the Surveillance, Epidemiology, and End Results (SEER) Program in order to estimate cancer incidence and patient survival in the United States. SEER collects cancer incidence data in nine geographic areas with a combined population of approximately 9.6 percent of the entire U.S. population. In this chapter, data from SEER are used to show cancer incidence in the United States by primary cancer site, race, sex, age, and year

Background and Data Sources

of diagnosis. The incidence rates presented are age-adjusted to the U.S. 1970 standard population. An exception is when SEER rates are compared to international incidence rates, in which case they are adjusted to the world standard. Incidence trends are presented for 1973 to 1991. Two measures to evaluate trends are given: (1) the estimated annual percent change (EAPC) and (2) the percent change. The EAPC is calculated by linear regression fit through the logarithms of the annual rates. The percent change is calculated between the average of the 1973 and 1974 rates and the average of the 1990 and 1991 rates. Survival data from SEER are presented for patients diagnosed in 1974–76, 1977–79, 1980–82, and 1983–90. Survival data from the End Results Program of NCI are provided for the periods 1960–63 and 1970–73. Because the earlier data are not population-based (except in Connecticut), these data and SEER are not strictly comparable, but each represents the best data available for that time period. Relative survival rates are expressed as percents, representing the proportion of patients who had not died from causes associated with their cancer 5 years after diagnosis.

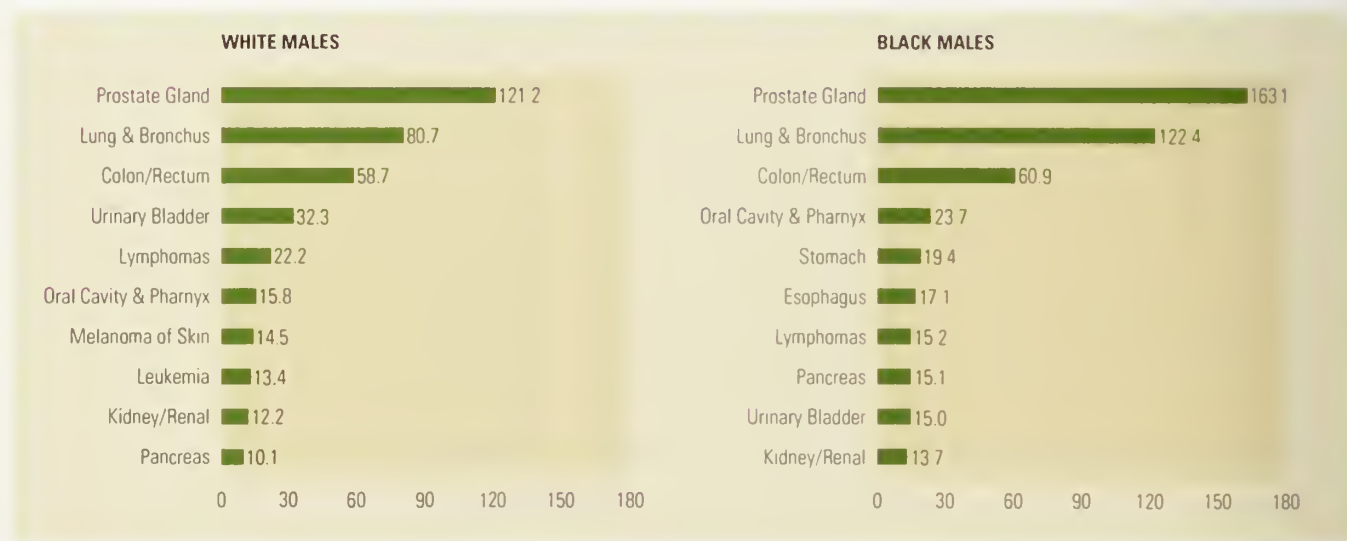
U.S. mortality rates over time are presented by age from 1973 to 1991 and by cancer site and sex from 1950 to 1991. The primary data source is the National Center for Health Statistics (NCHS) public use files as analyzed by the National Cancer Institute. Early data analyses are from NCI Monograph No. 59 (McKay, 1982); those for more recent years are analyses by SEER of the NCHS mortality files. The U.S. mortality rates are age-adjusted to the U.S. standard population in 1970. When U.S. rates are compared to international mortality rates, they are adjusted to the world standard.

Cancer Incidence in the United States (SEER)¹, 1987–91

10 Most Common Cancers by Sex Among Whites and Blacks

Since lung cancer incidence rates have reached an apparent plateau and prostate cancer has increased dramatically, cancer of the prostate gland has become the most common type of cancer among both black and white males. The black male prostate cancer incidence rate of 163.1 per 100,000 is 35 percent higher than that for white males, 121.2. Lung cancer and colorectal cancer rates are the second and third highest, respectively, for both black and white males. Bladder cancer is the fourth most commonly diagnosed cancer in white males, but ranks only ninth for black males.

Age-adjusted Cancer Incidence Rates, 1987–1991: 10 Most Common Sites by Race for Males



Incidence rates per 100,000 (age-adjusted to 1970 U.S. standard)

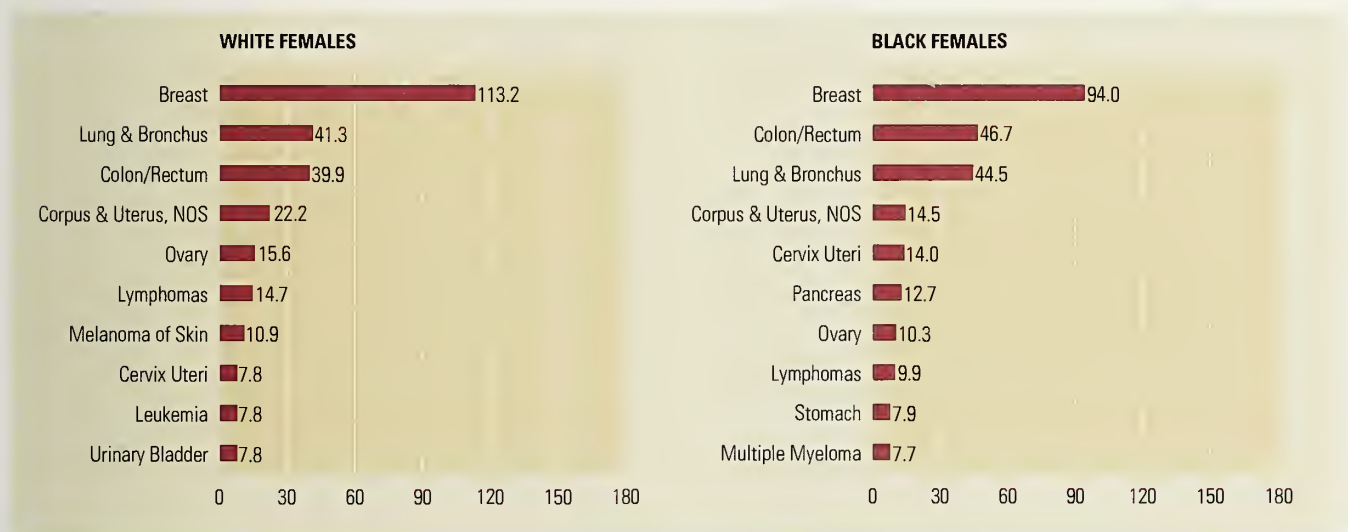
¹ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

Breast cancer is by far the most common cancer among both white and black females. It occurs more frequently among white females (113.2 per 100,000) than among black females (94.0 per 100,000). Lung cancer and colorectal cancer are the second and third highest cancers, respectively, among white females compared to ranks of third and second highest, respectively, for black females. Even though lung and colorectal cancers are two of the most common cancers among females, their incidence is much lower than that for males. The fourth most common cancer for females is corpus uteri for both whites and blacks. Even though the rank is the same, the rate for corpus cancer is higher among whites than blacks, unlike cancer of the cervix uteri, where the rate is higher among black females.

Cancer Incidence in the United States (SEER)¹, 1987–91

10 Most Common Cancers by Sex Among Whites and Blacks

Age-adjusted Cancer Incidence Rates, 1987–1991: 10 Most Common Sites by Race for Females



Incidence rates per 100,000 (age-adjusted to 1970 U.S. standard)

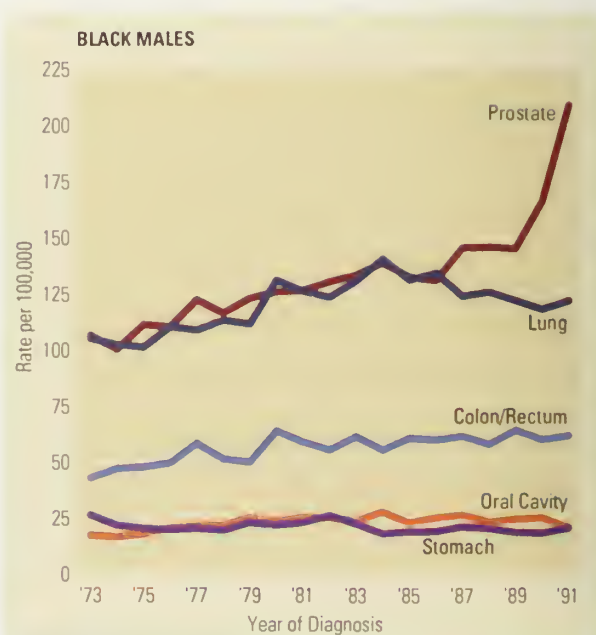
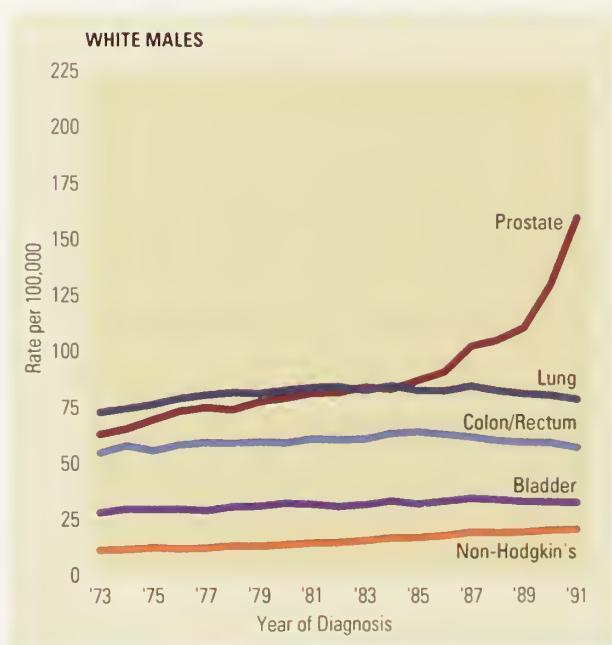
Cancer Incidence in the United States (SEER)², 1973–91

Changing Pattern for Major Cancers by Sex Among Whites and Blacks

With the increase in prostate cancer and the leveling off of lung cancer incidence rates, prostate cancer became the number one cancer among white males in the mid-1980s and has increased dramatically since then. Colorectal cancer in white males increased slightly until the mid-1980s and then decreased.

For black males, the trends in prostate and lung cancer are similar to those for white males, but the rates are higher. Colorectal cancer has not decreased as it has for white males.

Top Five Cancer Incidence Sites: White and Black Males



Sites chosen are based on 1987–91 incidence rates

² Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

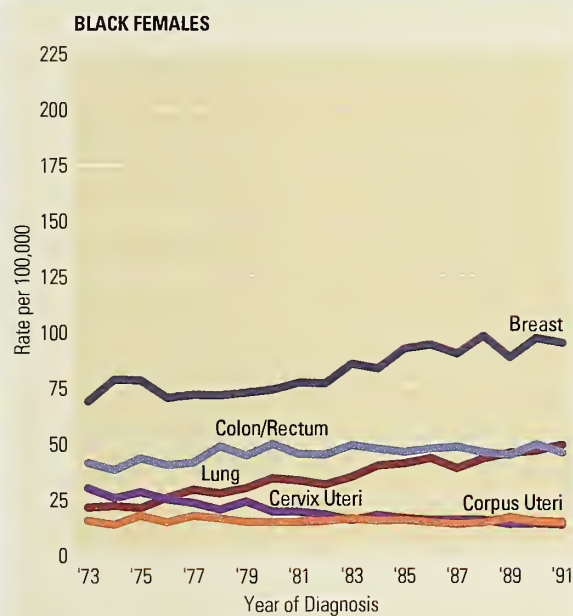
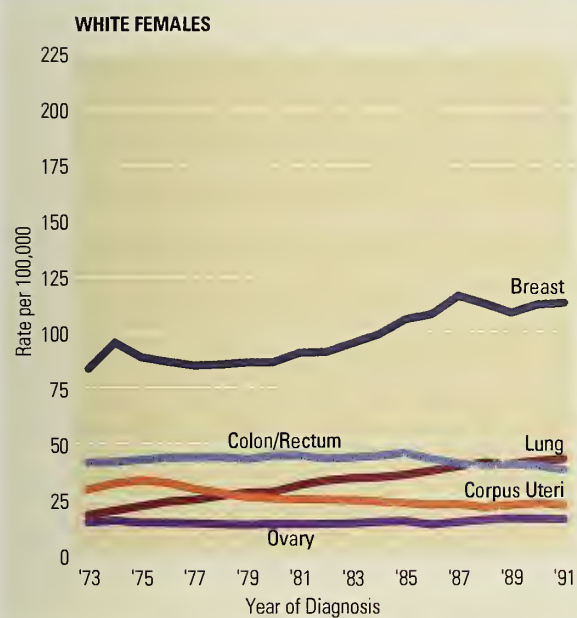
For white females, breast cancer has the highest incidence of any primary cancer site. Lung cancer increased 125 percent between 1973 and 1991 and now has the second highest incidence for white females. Cancer of the colon/rectum has decreased since the mid-1980s. Cancer of the corpus uteri has decreased.

For black females, breast cancer has the highest incidence of any primary cancer site, although the rate is less than that for white females. Lung cancer rates and trends are similar between white females and black females. Lung cancer only recently overtook colorectal cancer as the number two site for black females. Cancer of the cervix uteri has decreased and its rate is now similar to that of cancer of the corpus uteri.

Cancer Incidence in the United States (SEER)², 1973–91

Changing Pattern for Major Cancers by Sex Among Whites and Blacks

Top Five Cancer Incidence Sites: White and Black Females



Sites chosen are based on 1987–91 incidence rates

Cancer Incidence in the United States (SEER)³

Changing Patterns by Site Among All Races, Whites and Blacks, Males and Females

The incidence rates and trends by site for males and females, all races, white and black, for the time period 1973–1991 appear in these three charts. The data are from the SEER program of the NCI and are based on data published in the *SEER Cancer Statistics Review 1973–1991: Tables and Graphs* (Ries, 1994). Following are some highlights of the cancer incidence trends.

- Incidence rates for **all cancer sites combined** have increased for each race-sex group: 31 percent (white males), 15 percent (white females), 34 percent (black males), and 18 percent (black females).
- **Breast** cancer incidence in females increased from 88.6 per 100,000 in the early 1970s to 109.8 in the early 1990s. The incidence pattern for **breast** cancer varied with increases in the mid-1970s, decreases from the mid-1970s until the early 1980s, increases from the early 1980s until the late 1980s, and a leveling off of rates in the last couple of years.
- **Lung** cancer incidence is about 50 percent higher for black males than white males, but similar for white and black females.
- **Lung** cancer incidence increased approximately 125 percent among both black and white females. However, the rate of increase in 1975–79 of 6.2 percent per year slowed to 2.0 percent per year in 1987–91 for females of all races.
- Male **lung** cancer incidence rates declined by 1.7 percent per year for white males and 0.9 percent per year for black males over the most recent 5-year period, 1987–91. Between 1973 and 1991, a statistically significant decline in **lung** cancer incidence was limited to men under 55 years of age.
- **Colon/rectal** cancer incidence rates increased since 1973 but may have peaked for white males and females. Between 1987 and 1991, there were significant declines in incidence for both white males and white females. For black females, there was a nonsignificant decline between 1987 and 1991, and for black males, there was a nonsignificant increase.

³ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

SEER Incidence Rates and Trends for 1973–91^a, All Ages Combined

Cancer Site	Sex	Average Rate ^b		% Change 1973–91	EAPC ^c 1973–91
		1973–74	1990–91		
Brain & Other Nervous	Both Sexes	5.0	6.3	24.6	1.2 ^d
	Male	6.0	7.4	23.0	1.1 ^d
	Female	4.2	5.3	27.7	1.3 ^d
Breast	Both Sexes	48.3	60.1	24.5	1.8 ^d
	Male	1.0	0.9	-5.7	0.4
	Female	88.6	109.8	23.9	1.7 ^d
Cervix Uteri	Female	13.5	8.6	-36.4	-2.6 ^d
Colon & Rectum	Both Sexes	47.1	47.2	0.3	0.1
	Male	54.7	57.7	5.4	0.5 ^d
	Female	41.6	39.5	-5.0	-0.3
Corpus & Uterus, NOS	Female	29.6	21.4	-27.7	-2.4 ^d
Esophagus	Both Sexes	3.5	4.0	14.8	0.7 ^d
	Male	5.7	6.7	17.3	0.8 ^d
	Female	1.8	1.9	7.2	0.3
Hodgkin's Disease	Both Sexes	3.2	2.8	-11.7	-0.2
	Male	3.9	3.2	-18.4	-0.6 ^d
	Female	2.5	2.4	-2.7	0.3
Kidney & Renal Pelvis	Both Sexes	6.5	8.8	35.4	2.1 ^d
	Male	9.2	12.3	33.0	1.9 ^d
	Female	4.3	6.0	39.1	2.3 ^d
Larynx	Both Sexes	4.5	4.4	-3.0	-0.1
	Male	8.3	7.7	-7.2	-0.5 ^d
	Female	1.4	1.6	21.3	1.6 ^d
Leukemias	Both Sexes	10.7	9.5	-11.3	-0.4 ^d
	Male	14.0	12.3	-11.6	-0.4 ^d
	Female	8.2	7.3	-11.2	-0.5 ^d
Liver & Intrahep	Both Sexes	2.3	3.3	45.4	2.3 ^d
	Male	3.2	5.0	56.2	2.5 ^d
	Female	1.5	1.9	25.7	1.7 ^d
Lung & Bronchus	Both Sexes	43.2	58.1	34.4	1.7 ^d
	Male	73.9	80.3	8.7	0.5 ^d
	Female	19.1	41.6	118.0	4.6 ^d
Melanoma of Skin	Both Sexes	5.8	11.3	94.0	3.9 ^d
	Male	6.2	13.4	117.2	4.7 ^d
	Female	5.6	9.7	74.6	3.3 ^d
Multiple Myeloma	Both Sexes	3.8	4.4	15.9	0.8 ^d
	Male	4.5	5.6	25.3	1.0 ^d
	Female	3.3	3.4	5.5	0.6 ^d
Non-Hodgkin's Lymphoma	Both Sexes	8.7	15.1	72.8	3.3 ^d
	Male	10.2	18.7	83.6	3.8 ^d
	Female	7.5	11.9	57.4	2.7 ^d
Oral Cavity & Pharynx	Both Sexes	11.2	10.7	-4.7	-0.3 ^d
	Male	17.5	16.2	-7.4	-0.6 ^d
	Female	6.2	6.1	-0.9	-0.1
Ovary	Female	14.4	15.0	4.4	0.4
Pancreas	Both Sexes	9.8	8.8	-9.8	-0.4 ^d
	Male	12.2	10.0	-17.8	-1.0 ^d
	Female	7.9	7.8	-1.0	0.3
Prostate	Male	64.9	146.8	126.3	3.9 ^d
Stomach	Both Sexes	10.1	7.5	-26.0	-1.5 ^d
	Male	14.8	10.9	-26.3	-1.4 ^d
	Female	6.6	4.9	-24.6	-1.6 ^d
Testis	Male	3.1	4.5	42.7	2.2
Thyroid	Both Sexes	3.8	4.6	21.1	0.9 ^d
	Male	2.3	2.5	9.7	0.2
	Female	5.3	6.7	26.6	1.1 ^d
Urinary Bladder	Both Sexes	15.2	16.8	10.5	0.7 ^d
	Male	26.4	29.4	11.4	0.8 ^d
	Female	6.7	7.5	11.8	0.5 ^d
All Sites	Both Sexes	326.4	399.5	22.4	1.2 ^d
	Male	368.8	485.1	31.5	1.5 ^d
	Female	302.5	343.7	13.6	0.9 ^d

**Incidence Rates for
All Races,
per 100,000 U.S. Population
by Year, Site and Sex**

- ^a SEER program. Rates are per 100,000 and are age-adjusted to the 1970 U.S. standard population.
- ^b The Average Rate is the average annual rate over the specified 2-year period.
- ^c The EAPC is the Estimated Annual Percent Change over the 19-year interval.
- ^d The EAPC is significantly different from zero ($p < .05$).

Cancer Incidence in the United States (SEER)³

Changing Patterns by Site
Among All Races,
Whites and Blacks,
Males and Females

- Cancer of the **prostate** is the most commonly diagnosed cancer among males, the incidence rate having surpassed that for lung cancer in recent years. The incidence of **prostate** cancer increased 126 percent since 1973: 127 percent for white and 82 percent for black males. There is indirect evidence that the increasing incidence for this cancer may be due to increased detection of clinically asymptomatic cases associated with increasing rates of transurethral resection of the prostate (TURP) over the period 1973–86 and increasing use of testing with prostatic specific antigen (PSA) since the late 1980s.
- **Urinary bladder** cancer incidence increased for both blacks and whites. Higher percentage increases are noted for blacks than for whites.
- The incidence of **non-Hodgkin's lymphoma** (NHL) increased 74 percent for whites and 75 percent for blacks between 1973 and 1991.
- Although incidence rates for cancer of the **corpus uteri** are higher in white females than in black females, the difference has diminished over time. Trends in the incidence of cancer of the **corpus uteri** are markedly different in whites and blacks. From 1973 to 1991, white women experienced a 27 percent decline in incidence, while rates for black women remained virtually unchanged.
- Over the 19-year period 1973–91, the incidence of malignant **melanoma of the skin** among whites doubled. In contrast to the significant increase in incidence among whites of 5.3 percent each year over the period 1975–79, the trend over the last 5-year period, 1987 to 1991, shows a slowing of the rate of increase to 1.8 percent per year.
- Incidence rates for cancers of the **oral cavity and pharynx** increased 38 percent among black men and decreased 11 percent among white men over the period 1973–91.
- Overall incidence rates for **leukemia** appeared to decline in the period 1973–91, in each race and sex group.

³ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

SEER Incidence Rates and Trends for 1973–91^a, All Ages Combined

Cancer Site	Sex	Average Rate ^b		% Change 1973–91	EAPC ^c 1973–91
		1973–74	1990–91		
Brain & Other Nervous	Both Sexes	5.3	6.7	26.1	1.3 ^d
	Male	6.4	7.9	24.0	1.2 ^d
	Female	4.4	5.7	29.4	1.4 ^d
Breast	Both Sexes	49.2	61.7	25.3	1.8 ^d
	Male	0.9	0.9	-2.3	0.5
	Female	90.0	113.2	25.8	1.8 ^d
Cervix Uteri	Female	12.2	7.9	-35.4	-2.5 ^d
Colon & Rectum	Both Sexes	47.5	46.7	-1.6	0.0
	Male	55.7	57.4	3.0	0.3 ^d
	Female	41.7	38.9	-6.6	-0.4 ^d
Corpus & Uterus, NOS	Female	30.8	22.5	-27.0	-2.3 ^d
Esophagus	Both Sexes	3.0	3.5	17.9	0.8 ^d
	Male	4.9	5.9	20.5	1.0 ^d
	Female	1.6	1.7	7.4	0.2
Hodgkin's Disease	Both Sexes	3.3	3.1	-8.0	0.0
	Male	4.1	3.5	-14.5	-0.3
	Female	2.6	2.6	0.7	0.5
Kidney & Renal Pelvis	Both Sexes	6.5	8.9	36.8	2.1 ^d
	Male	9.3	12.4	32.3	1.9 ^d
	Female	4.3	6.1	43.0	2.4 ^d
Larynx	Both Sexes	4.4	4.3	-3.6	-0.1
	Male	8.3	7.5	-9.2	-0.6 ^d
	Female	1.3	1.6	24.3	1.6 ^d
Leukemias	Both Sexes	10.9	9.7	-11.0	-0.5 ^d
	Male	14.4	12.7	-12.2	-0.5 ^d
	Female	8.2	7.4	-10.2	-0.5 ^d
Liver & Intrahep	Both Sexes	2.0	2.6	31.2	1.7 ^d
	Male	2.7	4.0	44.1	2.0 ^d
	Female	1.4	1.6	11.7	1.2 ^d
Lung & Bronchus	Both Sexes	42.4	57.8	36.2	1.8 ^d
	Male	73.1	78.8	7.9	0.4 ^d
	Female	18.8	42.4	125.7	4.8 ^d
Melanoma of Skin	Both Sexes	6.3	12.7	101.6	4.1 ^d
	Male	6.7	15.0	123.5	4.8 ^d
	Female	6.0	11.1	83.1	3.5 ^d
Multiple Myeloma	Both Sexes	3.5	4.0	14.4	0.7 ^d
	Male	4.1	5.2	27.2	1.0 ^d
	Female	3.0	3.0	-0.1	0.4
Non-Hodgkin's Lymphoma	Both Sexes	8.9	15.6	74.4	3.4 ^d
	Male	10.5	19.3	84.0	3.9 ^d
	Female	7.7	12.3	59.5	2.7 ^d
Oral Cavity & Pharynx	Both Sexes	11.1	10.4	-6.7	-0.5 ^d
	Male	17.5	15.6	-11.2	-0.8 ^d
	Female	6.1	6.1	-0.1	0.0
Ovary	Female	15.0	15.8	5.7	0.5 ^d
Pancreas	Both Sexes	9.5	8.5	-9.8	-0.5 ^d
	Male	11.9	9.8	-17.7	-1.1 ^d
	Female	7.6	7.5	-1.7	0.2
Prostate	Male	63.5	144.2	127.1	4.0 ^d
Stomach	Both Sexes	9.3	6.4	-31.0	-1.9 ^d
	Male	13.6	9.4	-30.8	-1.8 ^d
	Female	6.0	4.2	-31.1	-2.1 ^d
Testis	Male	3.3	5.1	52.3	2.6 ^d
Thyroid	Both Sexes	3.6	4.7	29.2	1.2 ^d
	Male	2.1	2.6	19.6	0.8
	Female	5.0	6.8	34.5	1.4 ^d
Urinary Bladder	Both Sexes	15.9	17.9	12.8	0.8 ^d
	Male	28.0	31.7	13.2	0.9 ^d
	Female	6.9	7.8	13.0	0.6 ^d
All Sites	Both Sexes	325.7	400.7	23.0	1.2 ^d
	Male	367.9	482.4	31.1	1.4 ^d
	Female	303.6	349.0	15.0	0.9 ^d

**Incidence Rates for
Whites,
per 100,000 U.S. Population
by Year, Site and Sex**

^a SEER program. Rates are per 100,000 and are age-adjusted to the 1970 U.S. standard population.

^b The Average Rate is the average annual rate over the specified 2-year period.

^c The EAPC is the Estimated Annual Percent Change over the 19-year interval.

^d The EAPC is significantly different from zero ($p < .05$).

Cancer Incidence in the United States (SEER)³

Changing Patterns by Site
Among All Races,
Whites and Blacks,
Males and Females

- Incidence rates for cancer of the **pancreas**, a highly fatal cancer, declined somewhat in men.
- Cancer incidence for **kidney and renal pelvis** increased approximately 46 percent for blacks and 37 percent for whites.
- Incidence rates for **stomach** cancer continue to decline in each race and sex group.
- **Ovarian** cancer incidence rates increased among white women only slightly from 1973 to 1991. Most of the increase was due to the inclusion of borderline tumors since the mid-1980s.
- Incidence rates for invasive cancer of the **cervix uteri** have been declining among both white and black females. The rate of decline appears to be slowing in recent years. Between 1973 and 1991, incidence decreased 52 percent for black females and 35 percent for white females.
- **Laryngeal** cancer incidence rates continue to rise slowly in women: 1.6 percent per year for white females and 2.3 percent per year for black females. Incidence increased in black males (0.9 percent per year) and decreased in white males (0.6 percent per year).
- **Esophageal** cancer incidence rates are increasing more rapidly for males than females.

Incidence rates are presented for 1973–74 and 1990–91. Two measures to evaluate trends are given: (1) the estimated annual percent change (EAPC) and (2) the percent change. The EAPC is calculated by linear regression fit through the logarithm of the annual rates for each year 1973 to 1991. The percent change is calculated between the average of the 1973 and 1974 rates and the average of the 1990 and 1991 rates.

³ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

SEER Incidence Rates and Trends for 1973–91 ^a , All Ages Combined					
Cancer Site	Sex	Average Rate ^b		% Change 1973–91	EAPC ^c 1973–91
		1973–74	1990–91		
Brain & Other Nervous	Both Sexes	3.1	3.6	14.9	1.2
	Male	3.5	4.4	22.8	1.3
	Female	2.8	3.1	11.1	1.6
Breast	Both Sexes	40.9	55.0	34.5	2.1 ^d
	Male	2.1	1.1	-48.8	0.2
	Female	73.8	96.1	30.3	1.9 ^d
Cervix Uteri	Female	27.5	13.3	-51.7	-4.3 ^d
Colon & Rectum	Both Sexes	41.8	52.9	26.6	1.2 ^d
	Male	44.7	60.8	36.1	1.7 ^d
	Female	39.5	47.4	20.0	0.9 ^d
Corpus & Uterus, NOS	Female	14.0	14.3	2.0	-0.3
Esophagus	Both Sexes	10.1	10.3	1.5	0.1
	Male	16.1	17.5	9.0	0.3
	Female	4.9	4.8	-2.0	0.4
Hodgkin's Disease	Both Sexes	2.5	2.4	-0.1	-0.2
	Male	3.3	2.6	-20.4	-1.5
	Female	1.7	2.2	34.1	2.1
Kidney & Renal Pelvis	Both Sexes	6.5	9.5	46.2	2.8 ^d
	Male	8.6	14.3	65.4	3.3 ^d
	Female	4.8	6.0	26.4	2.6 ^d
Larynx	Both Sexes	6.1	7.1	15.8	0.9 ^d
	Male	10.9	13.2	21.4	0.9 ^d
	Female	2.1	2.5	17.8	2.3 ^d
Leukemias	Both Sexes	10.0	8.3	-17.0	-0.4
	Male	12.6	10.1	-19.4	-0.4
	Female	8.0	7.0	-12.7	-0.5
Liver & Intrahep	Both Sexes	3.5	5.1	44.7	1.8 ^d
	Male	5.8	8.2	40.6	2.2 ^d
	Female	1.7	2.8	61.3	1.4
Lung & Bronchus	Both Sexes	59.0	77.9	32.2	1.9 ^d
	Male	103.7	120.1	15.8	1.2 ^d
	Female	21.3	47.7	124.2	4.9 ^d
Melanoma of Skin	Both Sexes	0.6	0.8	42.2	0.4
	Male	0.4	1.2	223.2	2.3
	Female	0.7	0.6	-22.1	-1.1
Multiple Myeloma	Both Sexes	9.1	9.5	4.4	0.6
	Male	11.4	11.7	3.2	0.7
	Female	7.3	8.0	9.2	0.5
Non-Hodgkin's Lymphoma	Both Sexes	6.5	11.4	75.0	3.8 ^d
	Male	8.3	14.7	78.0	3.8 ^d
	Female	5.0	8.7	72.3	4.0 ^d
Oral Cavity & Pharynx	Both Sexes	10.9	13.4	22.7	1.1 ^d
	Male	16.4	22.7	38.3	1.8 ^d
	Female	6.2	6.1	-0.6	-0.3
Ovary	Female	10.3	10.1	-1.7	0.2
Pancreas	Both Sexes	14.2	13.0	-9.0	-0.1
	Male	17.3	14.9	-13.5	-0.6
	Female	11.9	11.5	-3.0	0.5
Prostate	Male	103.4	188.1	81.9	2.8 ^d
Stomach	Both Sexes	15.8	12.4	-21.7	-1.0 ^d
	Male	23.6	19.1	-19.1	-0.9
	Female	9.7	7.7	-20.9	-0.9
Testis	Male	0.9	0.7	-28.5	0.0
Thyroid	Both Sexes	2.7	2.8	5.8	-0.6
	Male	1.3	1.6	22.7	-0.8
	Female	3.8	3.8	-0.8	-0.7
Urinary Bladder	Both Sexes	7.9	10.0	25.9	0.7
	Male	11.5	14.8	28.5	1.0
	Female	4.9	6.6	33.9	0.7
All Sites	Both Sexes	351.1	434.1	23.6	1.2 ^d
	Male	434.3	581.3	33.9	1.6 ^d
	Female	285.9	336.5	17.7	1.1 ^d

**Incidence Rates for
Blacks,
per 100,000 U.S. Population
by Year, Site and Sex**

- ^a SEER program. Rates are per 100,000 and are age-adjusted to the 1970 U.S. standard population.
- ^b The Average Rate is the average annual rate over the specified 2-year period.
- ^c The EAPC is the Estimated Annual Percent Change over the 19-year interval.
- ^d The EAPC is significantly different from zero ($p < .05$).

Cancer Incidence in the United States (SEER)⁴

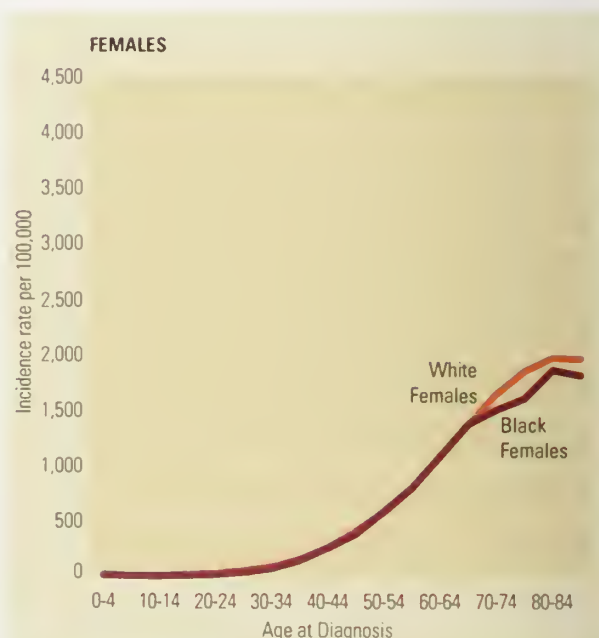
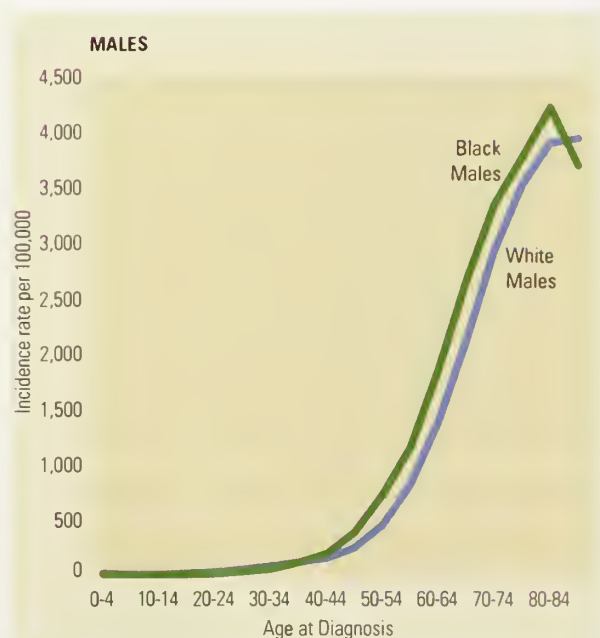
Age-specific Rates

All Sites

by Age and Race

Cancer, chiefly a disease of older people, is very rare in children and young adults. Less than half of cases are diagnosed before the age of 65. The rates for each race-sex group increase as age increases from childhood to the mid-80s. The rates peak for black males at age 80–84 when incidence is more than 4,000 per 100,000, at age 85 and above for white males, when incidence is slightly less than 4,000 per 100,000, and at age 80–84, for both white females and black females, when incidence is slightly less than 2,000 per 100,000. The rates for black males between ages 50 and 84 are much higher than those for the other race-sex groups in corresponding age groups. For ages 60 and over, the rates for white males, while lower than those for black males, are much higher than those for white or black females. The rates for white females and black females also increase with age but not as rapidly as those for their male counterparts. The rates for white females are similar to those for black females until age 70 and older, when they are slightly higher.

Average Annual Age-specific Cancer Incidence Rates, All Sites Combined, by Race and Sex, 1987–91



⁴ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

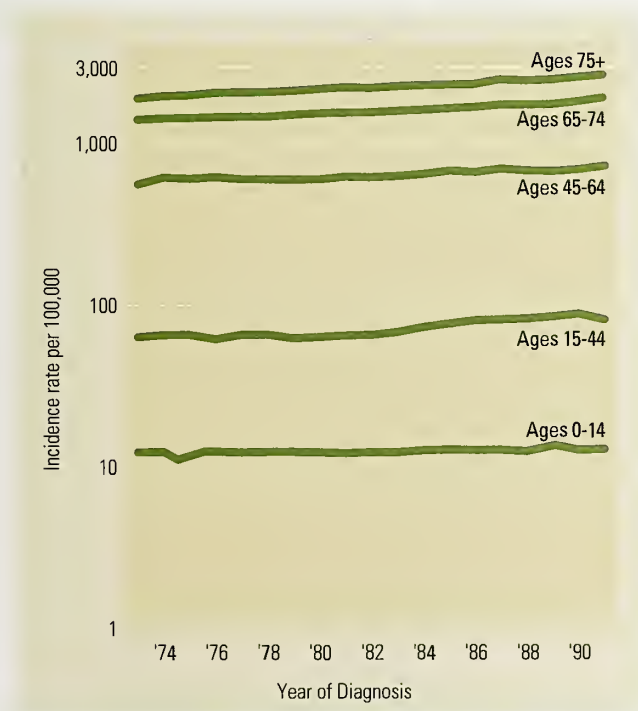
Data in this graph are on a logarithmic scale to display the trends in cancer incidence by five different age groups between 1973 and 1991; the log scale permits one to observe rates of change over time. Increases in incidence were seen for each age group. The largest increases in cancer incidence, however, were seen for the older groups (65–74 and 75 and over), where rates increased 35 percent and 28 percent, respectively, between 1973 and 1991. This graph emphasizes that cancer incidence is increasing for each age group, but more rapidly in older people than in the younger age groups. In addition, the graph emphasizes that older people have the highest cancer rates. The incidence rates range from less than 15 per 100,000 for those under 15 years of age to more than 2,000 per 100,000 for those 75 and over.

Cancer Incidence in the U.S. (SEER)⁵ Time Trends (1973–91)

All Sites

by Age Group for All Races
and Both Sexes

**Age-adjusted Cancer Incidence Rates by Age Group, All Sites Combined,
All Races, Both Sexes, 1973–91**



⁵ Source: SEER Program, NCI, based on an approximate 10 percent sample of the U.S. population

International Range of Cancer Incidence

Although cancer occurs in every country in the world, there are wide geographic variations in incidence. The rates presented are from *Cancer Incidence in Five Continents (CI5), Volume VI* (Parkin, 1992). The rates are age-adjusted to the world standard. Because many countries do not have national incidence rates, or have rates only for specific regions, there are fewer countries represented in the incidence data than in the mortality data. The tables show the wide range of incidence for selected cancer sites for males and females separately. The country/geographic area with the highest rate is shown together with the rate and the specific ethnic or racial group in which it occurred, if noted. Similarly, the lowest rates are given, as well as a ratio of the highest to the lowest.

For males, incidence rates for all sites combined ranged from 493.8 per 100,000 in Tasmania, Australia, to a low of 59.1 in The Gambia. Rates for U.S. males were 351.3 for blacks (SEER) and 330.4 for whites (SEER).

The largest ratios of the highest rates to the lowest rates in worldwide cancer incidence among males were for melanoma of the skin, nasopharynx, and larynx, with ratios of 289, 285, and 204, respectively. For melanoma of the skin, the area reporting the highest rate was the Australian Capital Territory with 28.9 per 100,000; the lowest rate, 0.1, was reported among Kuwaitis in Kuwait and among persons in Khon Kaen, Thailand. For nasopharynx, the highest rate was 28.5 in Hong Kong while the lowest was 0.1 for Quito, Ecuador. For larynx, the highest rate was 20.4 in Basque Country, Spain, and the lowest rate, 0.1, was for men in Qidong, China.

The worldwide range in lung cancer incidence among men ranges from a high of 119.1 in New Zealand Maoris to 1.0 per 100,000 in The Gambia. U.S. black men in New Orleans experienced a lung cancer rate of 115.9, just lower than that for Maoris in New Zealand. Prostate cancer rates were highest for black men in Atlanta, Georgia (102.0) and lowest in Qidong, China (0.8 per 100,000).

**International Range of
Incidence for Selected Sites
of Cancer Around 1985,
Males**

MALES					
Site	High		Low		Ratio
	Population	Rate	Population	Rate	H/L
Lip	Australia, South	13.5	Japan, Hiroshima U.S., Detroit: Black India, Bangalore	0.0	—
Tongue	Bermuda: Black	16.3	China, Qidong U.S., Los Angeles: Filipino The Gambia	0.2	81.5
Mouth	France, Bas Rhin	13.5	The Gambia	0.3	45.0
Oropharynx	France, Bas Rhin	12.5	China, Qidong	0.0	—
Nasopharynx	Hong Kong	28.5	Ecuador, Quito	0.1	285.0
Hypopharynx	France, Bas Rhin	15.2	China, Qidong	0.0	—
Esophagus	France, Calvados	26.5	U.S., Los Angeles: Filipino Israel: Born Israel	0.6	44.2
Stomach	Japan, Yamagata	93.3	India, Ahmedabad	2.1	44.4
Colon	U.S., Hawaii: Japanese	37.2	The Gambia	0.7	53.1
Rectum	Czech., Boh. & Morav.	22.9	The Gambia	0.7	32.7
Liver	Thailand, Khon Kaen China, Qidong	90.0	Netherlands, Maastricht	0.8	112.5
Gallbladder, etc.	Japan, Nagasaki	8.0	India, Bangalore India, Ahmedabad	0.4	20.0
Pancreas	U.S., California- Alameda: Black	13.7	The Gambia	0.4	34.3
Larynx	Spain, Basque Country	20.4	China, Qidong	0.1	204.0
Bronchus, Lung	New Zealand: Maori	119.1	The Gambia	1.0	119.1
Melanoma of Skin	Australian Capital Territory	28.9	Kuwait: Kuwaitis Thailand, Khon Kaen	0.1	289.0
Prostate	U.S., Atlanta: Black	102.0	China, Qidong	0.8	127.5
Testis	Switzerland, Zurich	8.8	The Gambia	0.2	44.0
Penis	Paraguay, Asunción	4.2	Japan, Yamagata Japan, Saga U.S., Los Angeles: Filipino U.S., Hawaii: Filipino Israel: Born Eur. Amer. U.S., Hawaii: Japanese Israel: All Jews	0.1	42.0
Bladder	Italy, Trieste	34.0	U.S., Los Angeles: Filipino The Gambia India, Madras	1.8	18.9
Kidney, etc.	Italy, Trieste	15.5	Algeria, Sétif	0.2	77.5
Brain, Nervous System	Sweden	10.7	Mali, Bamako	0.1	107.0
Thyroid Gland	U.S., Hawaii: Chinese	8.1	China, Qidong The Gambia	0.1	81.0
Non-Hodgkin's Lymphoma	U.S., California- Bay Area: White	17.4	Mali, Bamako	1.4	12.4
Hodgkin's Disease	Italy, Parma	4.5	China, Qidong Japan, Yamagata	0.1	45.0
Multiple Myeloma	U.S., Detroit: Black	9.0	Algeria, Sétif	0.2	45.0
Lymphoid Leukemia	Australian Cap. Terr.	8.1	China, Qidong	0.5	16.2
Myeloid Leukemia	U.S., Hawaii: Filipino	5.8	The Gambia	0.4	14.5
All Sites	Australia, Tasmania	493.8	The Gambia	59.1	8.4

Rates are age-adjusted to the world standard.

Source: Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. *Cancer Incidence in Five Continents*, Volume VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, France, 1992

International Range of Cancer Incidence

For females, rates for all sites ranged from a high of 345.4 per 100,000 in British Columbia, Canada, to a low of 39.6 in The Gambia. The comparable rate for U.S. white females (SEER) was 277.0 and for black females (SEER) was 227.1 per 100,000.

For females, liver and melanoma of the skin were sites with the largest high-to-low ratios in worldwide incidence, 383 and 253, respectively. The area reporting the highest liver cancer rate among women was Khon Kaen, Thailand (38.3 per 100,000); the lowest was 0.1 in Prince Edward Island (P.E.I.), Canada. For melanoma of the skin, the highest rate was 25.3 in Australian Capital Territory, while the lowest rate, 0.1, was reported by three areas: Qidong, China; non-Kuwaitis in Kuwait; and Sétif, Algeria.

Incidence rates for female breast cancer were highest among white women in the San Francisco Bay, California, area (104.2) and lowest among women in The Gambia (3.4 per 100,000). Lung cancer rates among women ranged from a high of 62.2 per 100,000 in New Zealand Maoris to a low of 1.4 in Madras, India. Colorectal cancer rates among women were highest in New Zealand non-Maoris (42.8 per 100,000) and hardly measurable among women in The Gambia (0.7).

International Range of Incidence for Selected Sites of Cancer Around 1985, Females

FEMALES					
Site	High		Low		Ratio
	Population	Rate	Population	Rate	
Lip	Thailand, Khon Kaen	3.8	China, Qidong Japan, Osaka China, Tianjin Switzerland, Basel U.K., North Western	0.0	—
Tongue	Singapore: Indian	3.0	Algeria, Sétif	0.0	—
Mouth	India, Bangalore	9.6	Japan, Yamagata Spain, Tarragona Poland, Warsaw Rural Algeria, Sétif	0.1	96.0
Oropharynx	U.S., California-Alameda: White	1.5	Japan, Yamagata Israel: Born in Africa, Asia	0.0	—
Nasopharynx	Hong Kong	11.2	Paraguay, Asunción U.S., Connecticut: Black Finland Japan, Nagasaki U.K., West Scotland U.K., Scotland Switzerland, Basel U.K., Birmingham Australia, South Canada, Maritime Provinces Japan, Yamagata Spain, Zaragoza Italy, Latina U.K., East Scotland U.K., S.E. Scotland Canada, New Brunswick U.S., Los Angeles: Span. surname white	0.1	112.0

**International Range of
Incidence for Selected Sites
of Cancer Around 1985,
Females (*continued*)**

FEMALES					
Site	High		Low		Ratio
	Population	Rate	Population	Rate	H/L
Nasopharynx (continued)			Israel: Born in Europe, America Israel: Non-Jews U.S., New Mexico U.S., Hawaii: Japanese Colombia, Cali Netherlands, Eindhoven Switzerland, Geneva France, Calvados Japan, Saga Canada, Nova Scotia U.K., N.E. Scotland		
Hypopharynx	India, Ahmedabad	2.2	Switzerland, Neuchâtel Italy, Torino Italy, Varese Poland, Lower Silesia	0.0	—
Esophagus	India, Bangalore	8.8	U.S., Los Angeles: Japanese	0.1	88.0
Stomach	Japan, Yamagata	42.9	India, Ahmedabad The Gambia	1.5	28.6
Colon	Bermuda: Black	34.4	Algeria, Sétif	0.9	38.2
Rectum	Israel: Born in Europe, America	16.1	The Gambia	0.6	26.8
Liver	Thailand, Khon Kaen	38.3	Canada, Prince Edward Island	0.1	383.0
Gallbladder, etc.	Peru, Trujillo	12.9	China, Qidong	0.4	32.3
Pancreas	U.S., California- Alameda: Black	11.9	India, Ahmedabad	0.2	59.5
Larynx	U.S., New Orleans: Black	3.8	Japan, Saga	0.1	38.0
Bronchus, Lung	New Zealand: Maori	62.2	India, Madras	1.4	44.4
Melanoma of Skin	Australian Capital Territory	25.3	China, Qidong Kuwait: Non-Kuwaitis Algeria, Sétif	0.1	253.0
Breast	U.S., California- Bay Area: White	104.2	The Gambia	3.4	30.6
Cervix Uteri	Peru, Trujillo	54.6	Israel: Non-Jews	2.6	21.0
Corpus Uteri	U.S., California- Bay Area: White	22.3	China, Qidong	0.5	44.6
Ovary, etc.	Switzerland, St. Gall	17.0	Mali, Bamako	1.0	17.0
Bladder	U.S., New Orleans: White	7.4	Algeria, Sétif	0.2	37.0
Kidney, etc.	Iceland	7.8	China, Qidong	0.4	19.5
Brain, Nervous System	Sweden	10.6	Algeria, Sétif Mali, Bamako	0.4	26.5
Thyroid Gland	U.S., Hawaii: Filipino	24.2	The Gambia	0.2	121.0
Non-Hodgkin's Lymphoma	Canada, Manitoba	10.6	Mali, Bamako	0.4	26.5
Hodgkin's Disease	U.S., Hawaii: Chinese	5.0	Japan, Hiroshima The Gambia	0.1	50.0
Multiple Myeloma	U.S., California; Alameda: Black	6.6	Peru, Trujillo Kyrgyzstan	0.1	66.0
Lymphoid Leukemia	U.S., Hawaii: Chinese	10.6	China, Qidong	0.3	35.3
Myeloid Leukemia	Italy, Romagna	5.3	China, Qidong The Gambia U.S., Hawaii: Chinese	0.3	17.7
All Sites	Canada, British Columbia	345.4	The Gambia	39.6	8.7

Rates are age-adjusted to the world standard.

Source: Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. *Cancer Incidence in Five Continents*, Volume VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, France, 1992

Cancer Survival Rates

Changes in the 5-Year
Relative Survival Rates
by Primary Cancer Site,
All Races

The overall 5-year relative survival rate for all cancer sites combined increased slightly from 49.3 percent in 1974–76 to 53.9 percent in 1983–90. Early data from 1960–63 and 1970–73 were not available for all races combined. Survival rates vary by primary site from less than 3 percent for cancer of the pancreas to more than 90 percent for cancer of the thyroid.

Part of the recent increase in breast cancer survival may be due to early detection; a higher percentage of the more recent cases were diagnosed with smaller tumors. Survival increases for prostate cancer may also in part be the result of early detection and the inclusion of occult disease in asymptomatic men.

5-Year Relative Survival Rates^a for Selected Cancer Sites, All Races

Cancer Site	ALL RACES					
	1960–63	1970–73	1974–76	1977–79	1980–82	1983–90
Brain & Other Nervous	—	—	22.3	24.4	25.0	27.3
Breast (females)	—	—	74.3	74.5	76.2	80.4
Cervix Uteri	—	—	68.5	67.7	66.9	67.4
Colon & Rectum	—	—	49.5	51.7	54.2	59.2
Corpus & Uterus, NOS	—	—	87.7	84.9	81.4	83.2
Esophagus	—	—	4.7	5.1	6.7	9.2
Hodgkin's Disease	—	—	71.1	73.0	74.3	78.9
Kidney & Renal Pelvis	—	—	51.3	50.8	51.4	56.3
Larynx	—	—	65.4	66.8	68.0	67.0
Leukemias	—	—	34.2	36.6	37.4	38.3
Liver & Intrahep	—	—	3.8	3.7	3.4	6.0
Lung & Bronchus	—	—	12.3	13.3	13.3	13.4
Melanoma of Skin	—	—	79.7	81.5	82.1	85.1
Multiple Myeloma	—	—	24.4	26.1	28.0	27.7
Non-Hodgkin's Lymphoma	—	—	47.1	48.1	51.1	52.0
Oral Cavity & Pharynx	—	—	53.2	52.4	52.4	52.3
Ovary	—	—	36.5	38.1	38.9	41.8
Pancreas	—	—	2.6	2.5	3.1	3.2
Prostate	—	—	66.7	70.9	73.1	79.6
Stomach	—	—	15.1	16.7	17.5	18.5
Testis	—	—	78.6	87.2	91.7	93.3
Thyroid	—	—	91.9	92.5	94.2	94.6
Urinary Bladder	—	—	72.4	74.8	77.9	79.8
All Sites	—	—	49.3	49.8	50.6	53.9

^a Data for 1960–63 and 1970–73 are from three hospital registries and one state registry and appear in *Cancer Patient Survival Experience, 1980*. Data for 1974–90 are from SEER, and represent approximately 10 percent of the U.S. population. Thus, the earlier data and the SEER data are not strictly comparable, but each represents the best available data for the period covered.

— Statistics could not be calculated.

The overall 5-year relative survival rate for all cancer sites combined among whites increased from slightly under 40 percent in the early 1960s to more than 55 percent in the mid- to late 1980s. The most dramatic increase in survival was for men with testicular cancer, where the survival rate reached 94 percent by the beginning of the decade. For nearly every cancer site, there has been an improvement in survival. The most recent data indicate that 82 percent of women diagnosed with breast cancer will survive their disease for more than 5 years. Lung cancer patients have low survival rates which have not increased in the last 10 years. More than 75 percent of patients with melanoma or Hodgkin's disease or cancer of the urinary bladder, corpus uteri, thyroid, breast, prostate, or testis survive at least 5 years after diagnosis.

Cancer Survival Rates

Changes in the 5-Year
Relative Survival Rates
by Primary Cancer Site,
Whites

5-Year Relative Survival Rates^a for Selected Cancer Sites, Whites

WHITES						
Cancer Site	1960–63	1970–73	1974–76	1977–79	1980–82	1983–90
Brain & Other Nervous	18	20	22.1	23.8	24.4	26.7
Breast (females)	63	68	74.9	75.2	76.9	81.6
Cervix Uteri	58	64	69.2	68.8	67.7	69.9
Colon & Rectum	—	—	49.8	52.1	54.7	60.1
Corpus & Uterus, NOS	73	81	88.6	86.2	82.7	84.9
Esophagus	4	4	5.1	5.6	7.4	10.5
Hodgkin's Disease	40	67	71.6	73.0	74.9	79.4
Kidney & Renal Pelvis	37	46	51.4	50.7	50.9	56.9
Larynx	53	62	66.2	68.1	69.1	69.1
Leukemias	14	22	34.8	37.5	38.3	39.5
Liver & Intrahep	—	—	4.3	3.2	3.9	6.6
Lung & Bronchus	8	10	12.4	13.6	13.5	13.7
Melanoma of Skin	60	68	80.0	81.8	82.3	85.3
Multiple Myeloma	12	19	24.1	24.6	27.9	27.4
Non-Hodgkin's Lymphoma	31	41	47.5	48.3	51.6	52.6
Oral Cavity & Pharynx	45	43	54.9	54.2	55.1	54.6
Ovary	32	36	36.3	37.5	38.7	41.6
Pancreas	1	2	2.6	2.3	2.8	3.0
Prostate	50	63	67.7	71.9	74.3	81.3
Stomach	11	13	14.4	16.0	16.2	17.5
Testis	63	72	78.6	87.7	91.8	93.6
Thyroid	83	86	91.9	92.3	93.8	94.7
Urinary Bladder	53	61	73.6	75.7	78.8	80.7
All Sites	39	43	50.3	50.8	51.8	55.5

^a Data for 1960–63 and 1970–73 are from three hospital registries and one state registry and appear in *Cancer Patient Survival Experience, 1980*. Data for 1974–90 are from SEER, and represent approximately 10 percent of the U.S. population. Thus, the earlier data and the SEER data are not strictly comparable, but each represents the best available data for the period covered.

— Statistics could not be calculated.

Cancer Survival Rates

Changes in the 5-Year Relative Survival Rates by Primary Cancer Site, Blacks

Even though survival rates have increased for a few cancers among blacks, the overall survival rate for all cancers combined has increased only slightly since the mid-1970s. The 5-year relative survival rate among blacks is only 40.4 percent compared to 55.5 percent among whites diagnosed in 1983–90. Overall survival rates may obscure the survival differentials by individual primary site. Whites survive more than 10 percentage points higher than blacks for cancer of the breast, cervix uteri, colon/rectum, corpus uteri, larynx, melanoma, oral cavity and pharynx, prostate, and urinary bladder. Differences in stage at diagnosis may account for some of these disparities, but other factors may have a role. Studies are under way at NCI to investigate explanatory factors for survival differences in several cancer sites.

5-Year Relative Survival Rates^a for Selected Cancer Sites, Blacks

Cancer Site	BLACKS					
	1960–63	1970–73	1974–76	1977–79	1980–82	1983–90
Brain & Other Nervous	19	19	26.8	27.7	30.7	30.6
Breast (females)	46	51	62.9	62.8	65.7	65.8
Cervix Uteri	47	61	63.5	61.9	60.4	56.4
Colon & Rectum	—	—	44.5	45.4	46.2	49.5
Corpus & Uterus, NOS	31	44	60.4	57.5	53.7	55.2
Esophagus	1	4	3.9	2.8	5.4	6.1
Hodgkin's Disease	—	—	68.3	73.1	71.6	74.1
Kidney & Renal Pelvis	38	44	48.9	51.4	55.0	52.0
Larynx	—	—	58.7	55.4	58.4	53.1
Leukemias	—	—	31.5	29.6	32.7	30.8
Liver & Intrahep	—	—	1.0	5.7	1.6	4.0
Lung & Bronchus	5	7	11.4	10.9	12.1	11.1
Melanoma of Skin	—	—	66.4	50.8	56.9	70.3
Multiple Myeloma	—	—	27.2	33.9	28.7	29.4
Non-Hodgkin's Lymphoma	—	—	47.9	50.4	50.1	45.4
Oral Cavity & Pharynx	—	—	36.3	36.3	30.5	33.6
Ovary	32	32	40.1	39.8	37.6	38.4
Pancreas	1	2	2.3	3.8	4.8	4.9
Prostate	35	55	58.0	62.1	64.4	66.4
Stomach	8	13	16.3	15.3	19.3	18.8
Testis	—	—	75.7	—	89.7	87.3
Thyroid	—	—	87.6	91.3	94.9	90.2
Urinary Bladder	24	36	47.8	54.9	58.3	60.0
All Sites	27	31	38.8	38.9	39.4	40.4

^a Data for 1960–63 and 1970–73 are from three hospital registries and one state registry and appear in *Cancer Patient Survival Experience, 1980*. Data for 1974–90 are from SEER, and represent approximately 10 percent of the U.S. population. Thus, the earlier data and the SEER data are not strictly comparable, but each represents the best available data for the period covered.

— Statistics could not be calculated.

Cancer incidence for all sites combined increased 10 percent between 1973 and 1991 for children. The increase was 10 percent among white children and 14 percent among black children. Soft tissue sarcoma and brain cancer incidence increased more than 25 percent. Acute lymphocytic leukemia showed an increase of 20 percent. The overall rate of leukemia remained flat, implying that the increase in acute lymphocytic leukemia may indicate that that type of leukemia has been specified more frequently over time.

Cancer among children is rare, only 14.1 cases per 100,000 children. Incidence is slightly higher among whites (14.4) than blacks (11.8 per 100,000). Leukemias (4.3 per 100,000) and cancer of the brain and other nervous system (3.4 per 100,000) account for more than half of the cancers among children.

Even though cancer incidence has increased, cancer mortality among children has decreased dramatically, by 42 percent. Cancer mortality has decreased among black as well as white children. Mortality has decreased for every cancer site; most have decreased by at least 50 percent.

Cancer survival rates have increased dramatically for children since the 1960s. For all sites combined, the 5-year relative survival rate has increased from less than 30 percent to nearly 70 percent. Among acute lymphocytic leukemia patients diagnosed during the early 1960s, less than 5 percent survived 5 years. For the most recent time, 1983–90, three-fourths survived their disease at least 5 years past diagnosis. Because long-term survival rates do not exist for all races combined, the table showing trends in survival presents rates for whites only.

5-Year Relative Survival Rates^a for Selected Cancers, Whites Under Age 15

WHITES UNDER AGE 15						
Cancer Site	1960–63	1970–73	1974–76	1977–79	1980–82	1983–90
All Sites	28	45	55.3	61.8	65.0	69.7
Acute Lymphocytic Leukemia	4	34	53.3	68.5	70.9	75.0
Acute Myeloid Leukemia	3	5	15.8	24.5	22.3	29.4
Bone & Joint	20	30	52.6	50.0	53.0	59.4
Brain & Nervous System	35	45	54.7	56.4	56.0	62.2
Hodgkin's Disease	52	90	80.2	84.6	91.1	89.5
Neuroblastoma	25	40	49.1	51.2	56.9	56.4
Non-Hodgkin's Lymphoma	18	26	43.2	49.2	58.5	72.0
Wilms' Tumor	33	70	74.2	80.1	83.2	87.6

^a Data for 1960–63 and 1970–73 are from three hospital registries and one state registry and appear in *Cancer Patient Survival Experience, 1980*. Data for 1974–90 are from SEER, and represent approximately 10 percent of the U.S. population. Thus, the earlier data and the SEER data are not strictly comparable, but each represents the best available data for the period covered.

Cancer Among Children Under Age 15

by Type of Cancer

Cancer Mortality in the United States

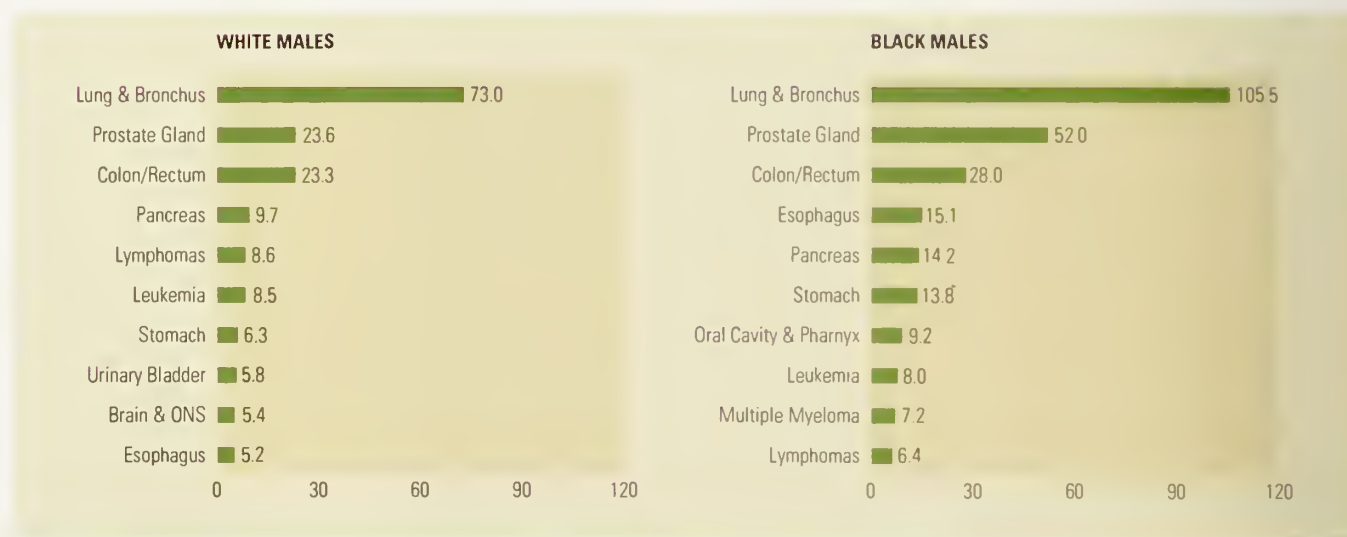
10 Most Common Cancer Deaths by Sex, Whites and Blacks

The number one cause of cancer death in the United States is cancer of the lung and bronchus. Even when analyzed by race and sex, lung cancer is number one for white males and females and for black males. For black females, breast cancer mortality is slightly higher than lung cancer.

For white males, the colon/rectal mortality is similar to that for prostate cancer (second and third, respectively). For black males, colon/rectal cancer mortality was also third, but the colon/rectal mortality rate is much less than that for prostate cancer. The mortality rates for esophagus, pancreas, and stomach are similar for black males.

MALES

Age-adjusted Cancer Death Rates, 1987–1991: 10 Most Common Sites by Race



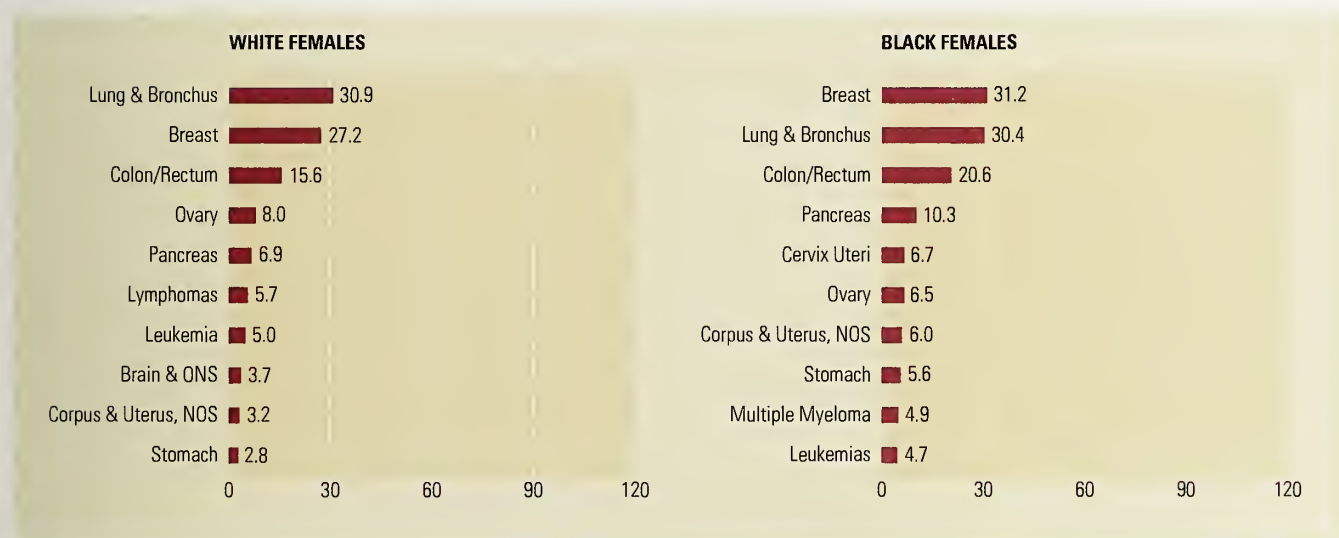
Mortality rates per 100,000 (age-adjusted to 1970 U.S. standard)

For both white and black females, the top three sites are lung, breast, and colon/rectal cancer. As noted above, however, breast cancer mortality is still slightly higher than lung cancer mortality for black females. If lung cancer trends continue upward, lung cancer mortality will surpass breast cancer for black females as it already has for white females.

Cancer Mortality in the United States

10 Most Common
Cancer Deaths by Sex,
Whites and Blacks

FEMALES
Age-adjusted Cancer Death Rates, 1987–1991: 10 Most Common Sites by Race



Mortality rates per 100,000 (age-adjusted to 1970 U.S. standard)

Source: NCHS public use tape

Cancer Mortality in the United States

Changing Patterns for
Major Cancers
in U.S. Males and Females,
1950–91

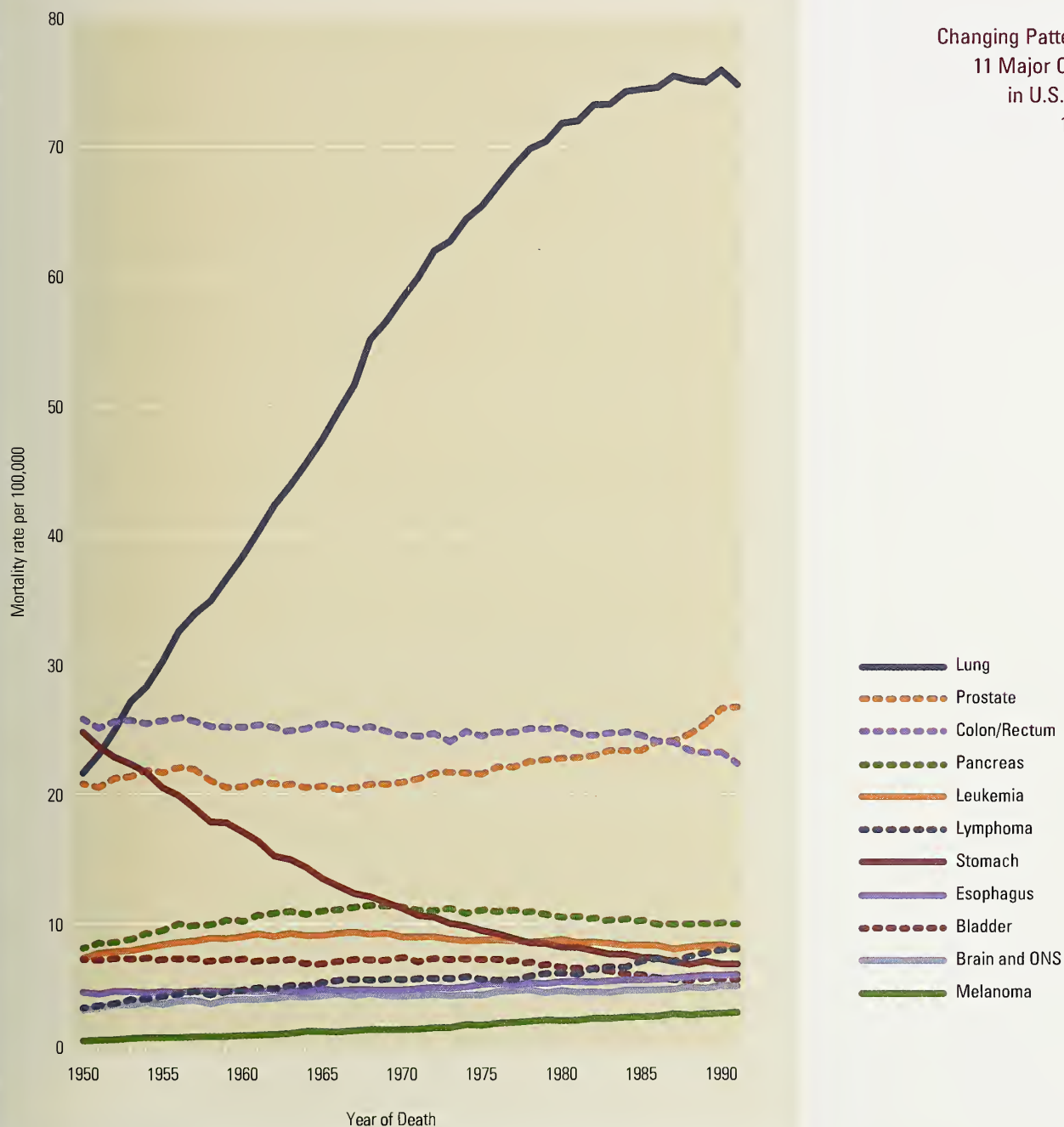
The lung cancer death rate increased dramatically between 1950 and the early 1980s. Since the mid-1980s, there has been a leveling off of the lung cancer death rate. Stomach cancer dropped dramatically, from the second highest death rate in 1950 to seventh highest in 1991. Mortality trends for prostate cancer began increasing slightly in the mid-1970s and began to increase more rapidly between 1985 and 1990. On the other hand, mortality rates due to colon/rectum cancer decreased between 1985 and 1990. These trends in opposite directions led to prostate cancer mortality becoming higher than colon/rectum cancer mortality in 1988.

Lung cancer mortality among U.S. women went from a rank of ninth in 1950 to number one by 1987, more than quadrupling between 1950 and 1991. For many years, the highest death rate of any cancer in women was breast cancer, but it was surpassed by lung cancer after 1986. Dramatic decreases in mortality occurred for cancers of the stomach, cervix uteri, and especially colon/rectum between 1950 and 1991.

Death Rates for Males, per 100,000, for 11 Sites, 1950–91, Age-adjusted to 1970 U.S. Standard

Cancer Mortality in the United States

Changing Patterns for
11 Major Cancers
in U.S. Males,
1950–91



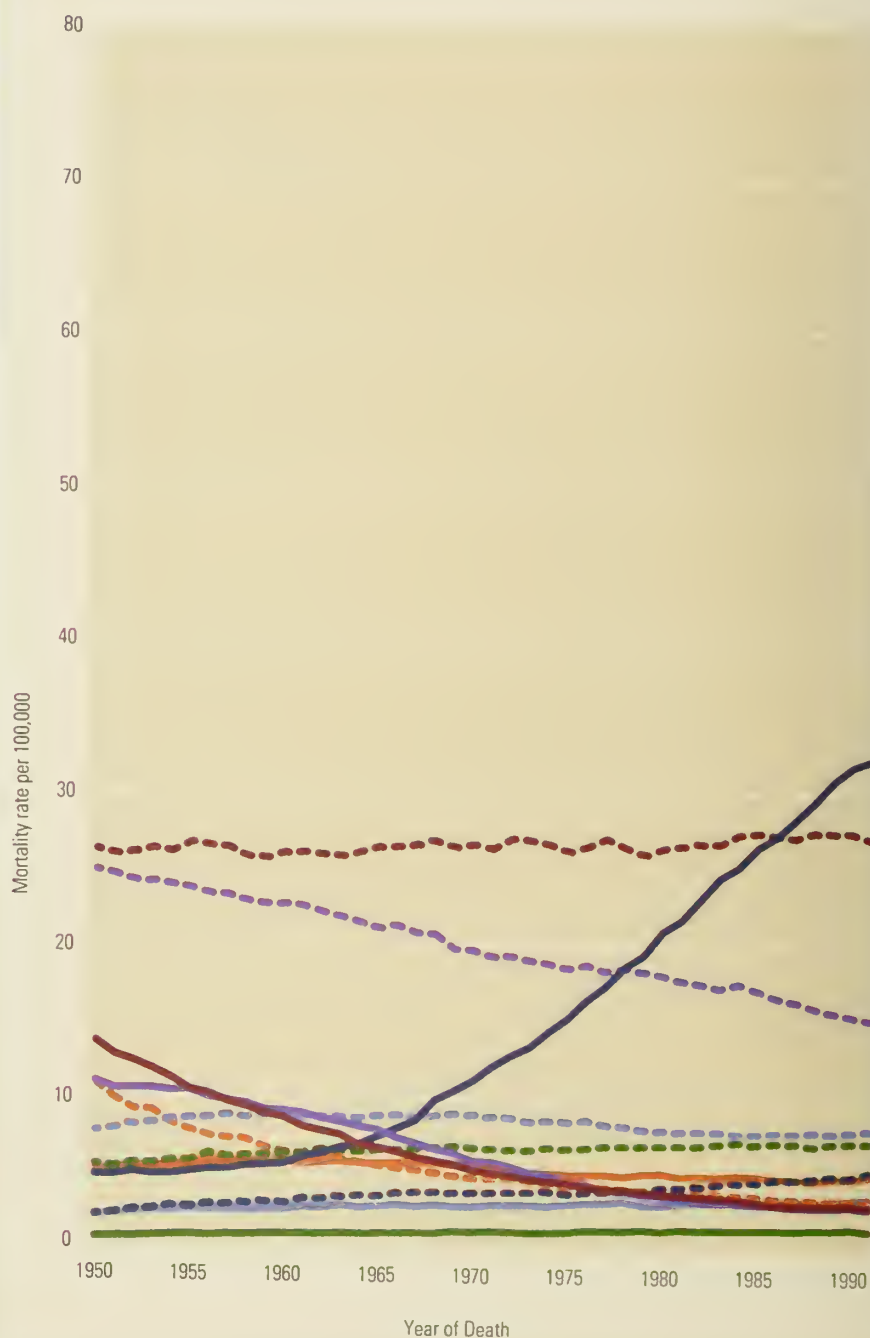
Source: NCHS public use file

Cancer Mortality in the United States

Changing Patterns for
12 Major Cancers
in U.S. Females,
1950–91

Death Rates for Females, per 100,000, for 12 Sites, 1950–91, Age-adjusted to 1970 U.S. Standard

- Lung
- - - Breast
- - - Colon/Rectum
- - - Ovary
- - - Pancreas
- - - Lymphoma
- Leukemia
- Brain and ONS
- - - Uterus
- Stomach
- Cervix
- Melanoma



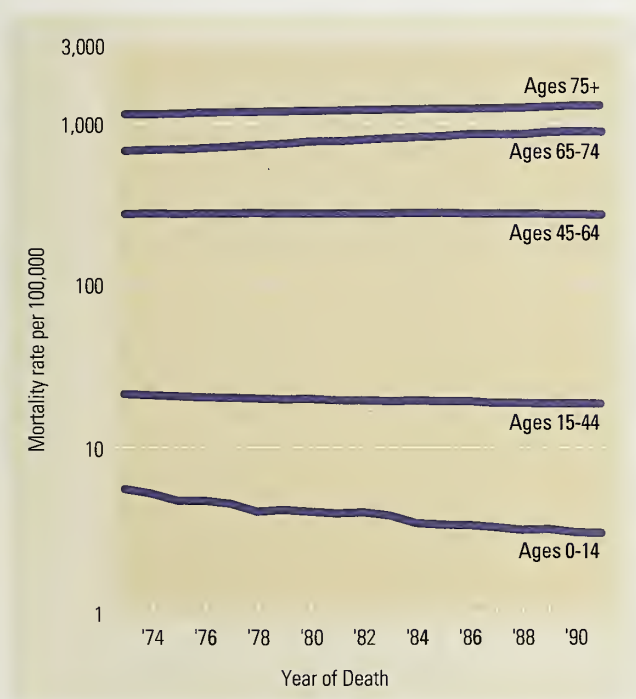
Source: NCHS public use file

Data in this graph are on a logarithmic scale to display the trends between 1973 and 1991 in cancer mortality (death rates) in the U.S. by five different age groups. Unlike the earlier incidence graph showing all increasing trends for each of the same age groups, this graph depicts some downward trends among younger Americans. The decrease in cancer mortality for children is dramatic, more than a 40 percent decrease since 1973. The 15–44 year-old age group also shows a decrease, but not as large. The 45–64 year-old age group showed little change in cancer mortality. This, however, is masking an 11 percent decrease for the 45–54 year-olds offset by a 4 percent increase for the 55–64 year-olds between 1973 and 1991 (data not shown in graph). There have been increases of 13.7 and 18.5 percent for the age groups 65–74 and 75 and over, respectively, for the same time period. Again, as in the incidence graph, this graph emphasizes the dual impact cancer has on older people. Not only are mortality rates much higher than in any other age group, but they are also increasing.

Cancer Mortality in the United States

Changing Cancer Patterns,
1973–91 by Age Group for
All Races and Both Sexes,
All Sites Combined

**Age-adjusted Mortality Rates, by Age Group, All Sites Combined,
All Races, Both Sexes, 1973–91**



Source: NCHS public use file

Cancer Death Rates Among 50 Countries

All Sites

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male and Female

Bar charts are presented for all cancer sites combined and several specific cancer sites. These charts depict the cancer mortality rates 1986–88 in 50 countries around the world. The rates used are the number of cancer deaths per 100,000 population and are age-adjusted to the world standard (Parkin, 1992).

The cancer mortality rates for each of the 50 countries are ranked from the highest to the lowest. Separate graphs are shown for males and females. There is a four-fold difference between the lowest (54.4 in Thailand) and highest (235.4 in Hungary) male cancer mortality rates. The difference between the lowest and highest rates for female cancer mortality is not as striking (36.4 in Thailand vs. 139.4 in Denmark), a little less than four-fold. For males, the United States ranks 24th (163.2 per 100,000) from the highest; for females, the United States ranks 17th (109.7 per 100,000) out of 50 countries. For both males and females, the cancer mortality rates for the United States are in the middle. Cancer mortality is generally higher among males. It should be noted that Thailand's mortality rates look unusually low in that they are low for every site presented.

The death rates for all cancer sites combined provide an overview of the burden of cancer by country and sex. Cancer death rates for specific cancers may vary widely among countries, and an overall rate may obscure these site-specific patterns. The dynamic nature of these overall demographic patterns and rates is better understood by comparing mortality rates for specific cancers.

Names of countries are as they were at the time the data were gathered and have not been updated to reflect political change.

- 1986 only
- 1986–87 only
- 1987 only
- 1987–88 only

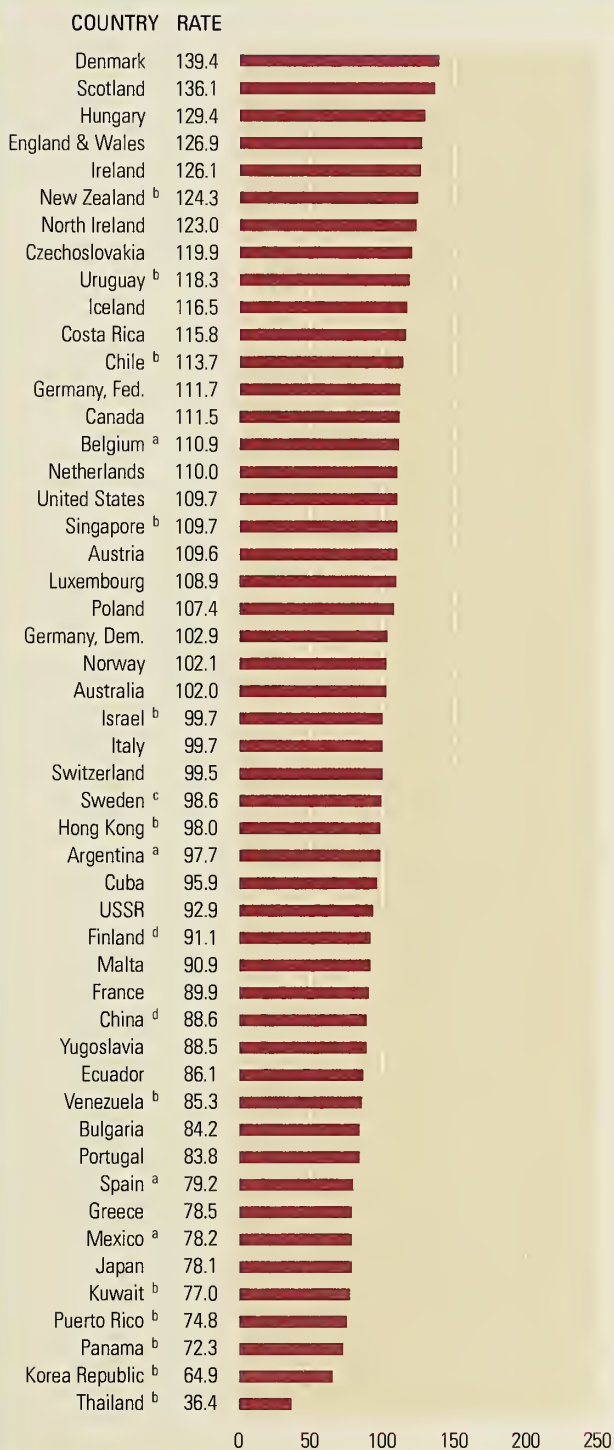
Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

All Sites Combined, Males



All Sites Combined, Females



Cancer Death Rates
Among 50 Countries

Lung

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male and Female

U.S. males rank 12th in lung cancer mortality, and females rank 4th. Generally, lung cancer mortality rates for men are substantially higher than those for women. In many countries, there is a seven-fold male-to-female difference in lung cancer mortality. For Iceland, the exception, rates for males and females are similar. Belgium has the highest lung cancer mortality rate for males; Scotland has the second highest for males and the highest for females. Deaths from lung cancer are relatively rare in Mexico and Central and South America. Within the United States, there is considerable variation in mortality by geographic area. For males, the highest mortality rates are in the South; for females, the highest rates are on the West Coast, Maine, Nevada, Kentucky, West Virginia, and Maryland.

^a 1986 only
^b 1986–87 only
^c 1987 only
^d 1987–88 only

Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Lung, Males



Lung, Females



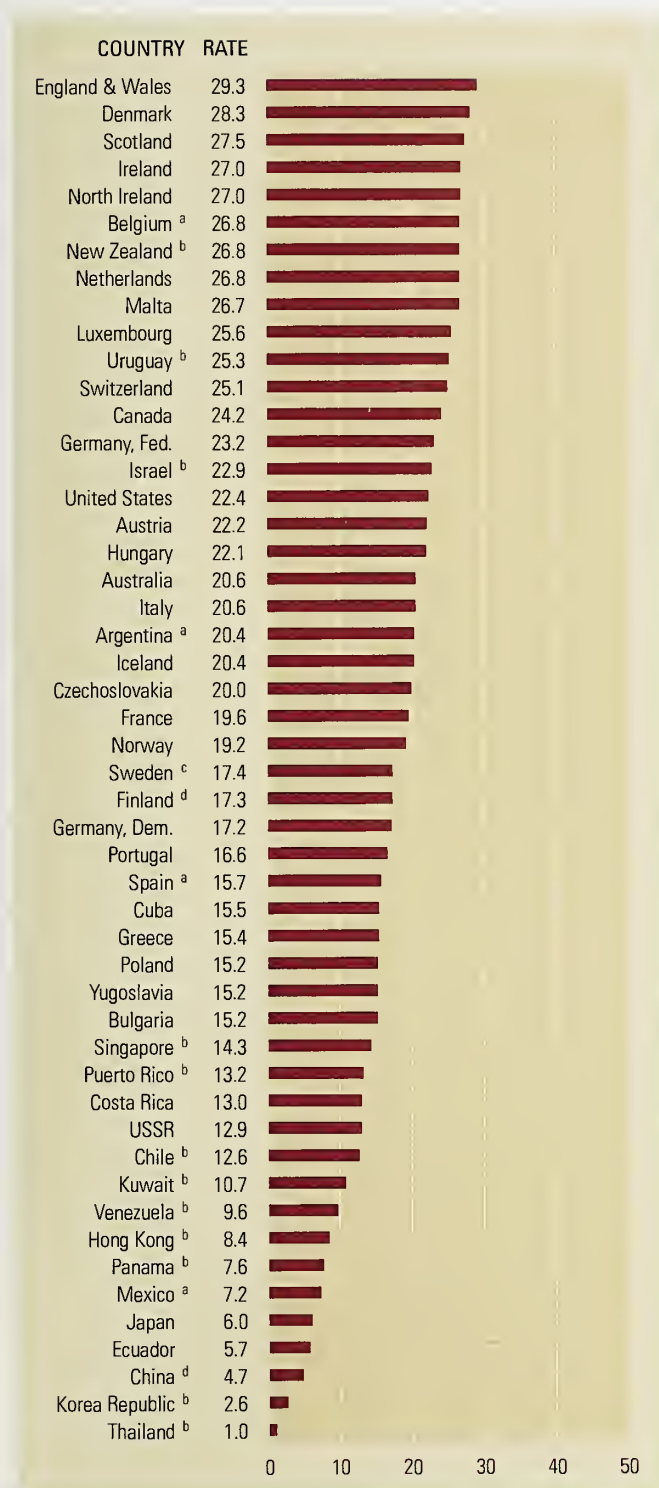
Cancer Death Rates Among 50 Countries

Breast

1986-88 Age-adjusted
Death Rates per
100,000 Population,
Female

For many years, breast cancer was the most common cause of cancer death among females in the United States until recently, when lung cancer mortality began to exceed breast cancer mortality. This phenomenon has been true for many years in Asian countries where deaths from breast cancer are rare and the incidence of breast cancer is low. In European countries, breast cancer death rates are higher than lung cancer. Breast cancer death rates are highest in England and Wales, followed by Denmark, Scotland, and Ireland. The United States ranks 16th. They are lowest in Asian countries.

Breast, Females

^a 1986 only^b 1986–87 only^c 1987 only^d 1987–88 only

Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Cancer Death Rates Among 50 Countries

Prostate

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male

Cancer of the prostate is one of the most common cancers among men. The lowest mortality rates were among Asian men, and the highest were in Switzerland. Some of the highest rates were seen in the Nordic countries. The prostate cancer mortality rate in the United States was in the middle, at 15.7 per 100,000. In the United States, even though cancer of the prostate is the most common incidence site in men, the mortality rate is less than one-third that for lung cancer. This is partly due to the fact that the prostate cancer survival rate is so much higher than that for lung cancer.

Prostate, Males



- ^a 1986 only
- ^b 1986–87 only
- ^c 1987 only
- ^d 1987–88 only

Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Cancer Death Rates Among 50 Countries

Colon and Rectum

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male and Female

Even though risk factors, incidence rates, and death rates are different for cancer of the colon and cancer of the rectum, the two are combined into colorectal cancer primarily because death certificates frequently do not accurately distinguish one from the other. Colorectal cancers are considered diseases of economically developed countries: death rates are highest in New Zealand and Europe and lowest in Thailand, Korea, Kuwait, Mexico, Ecuador, and Venezuela. The mortality rate for the United States ranks in the mid-range of rates from other countries. This, however, does not mean that all areas in the United States experience the same mortality; death rates for this disease are relatively high in the Northeast and low in the South and Southwest. For males, colorectal cancer deaths rank third after lung and prostate cancers. For females, breast and lung cancer deaths are higher than colorectal cancer. Death rates are higher among males than females.

- ^a 1986 only
- ^b 1986–87 only
- ^c 1987 only
- ^d 1987–88 only

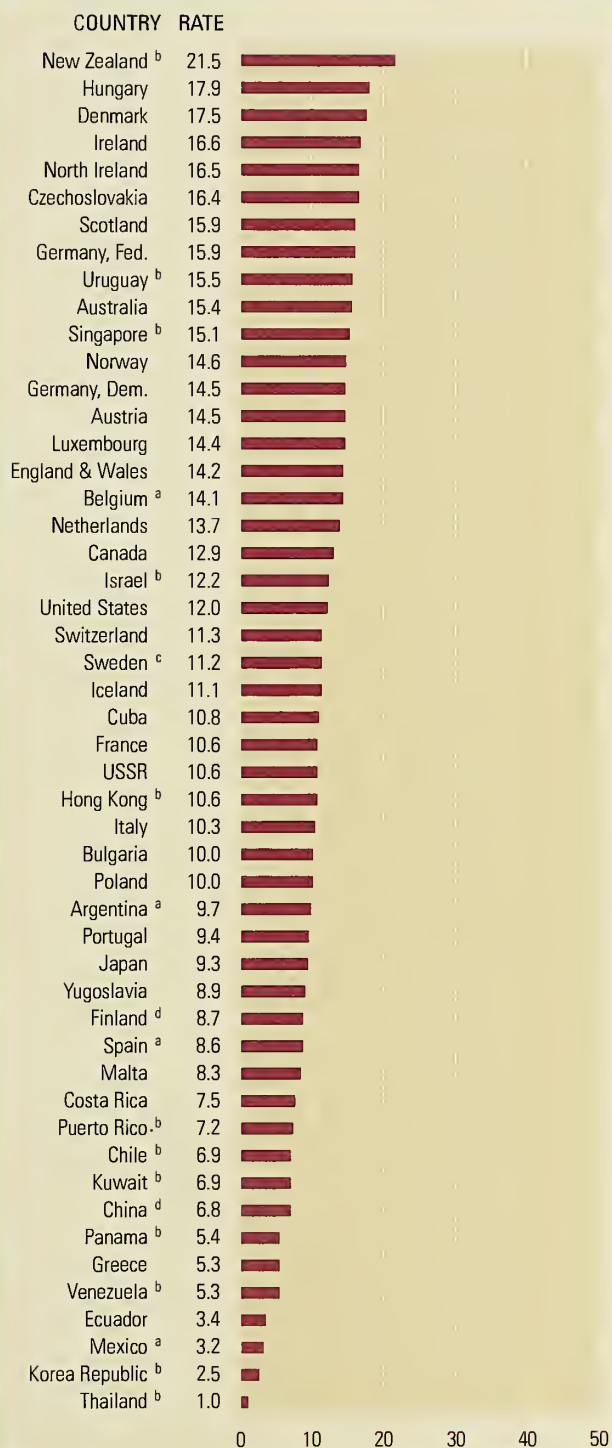
Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Colon and Rectum, Males



Colon and Rectum, Females



Cancer Death Rates Among 50 Countries

Stomach

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male and Female

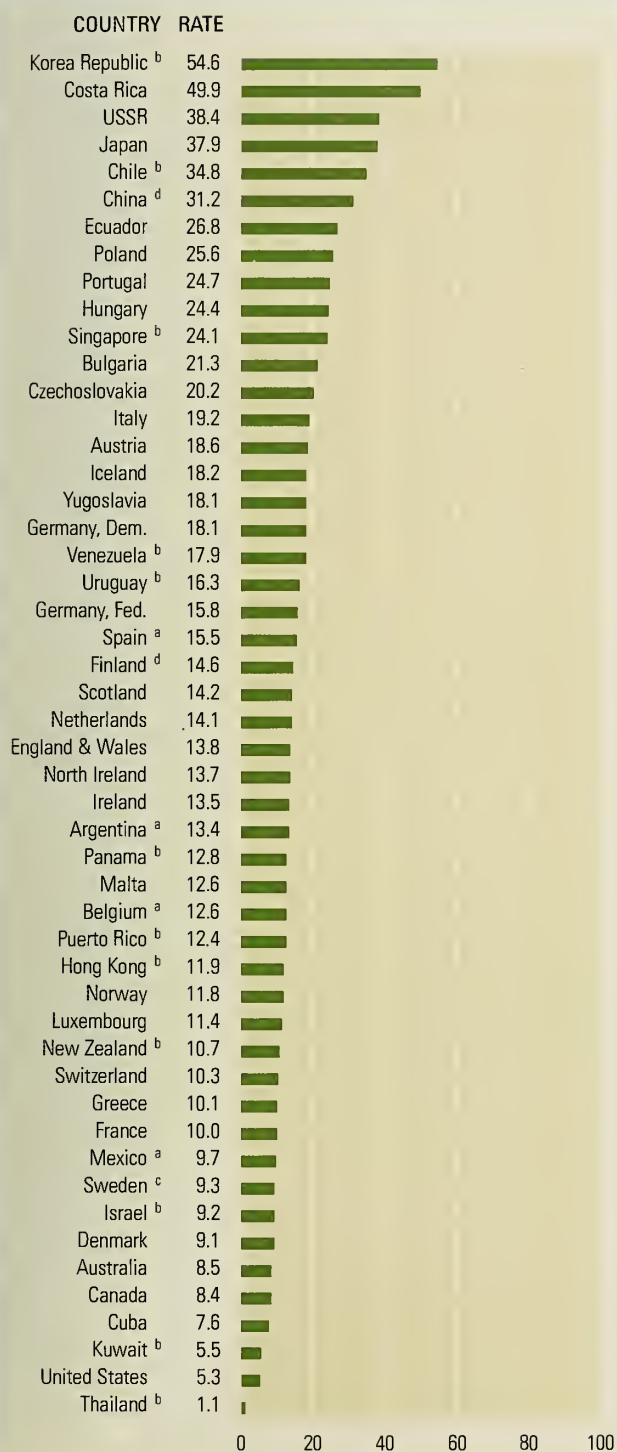
The United States has one of the lowest stomach cancer mortality rates in the world for both males and females: 5.3 for males and 2.3 for females. The highest rates around the world were noted in Asian countries, Costa Rica, the USSR, Chile, and Ecuador. Stomach cancer, which during the early 1930s had the highest mortality rate of any cancer in the United States, is now in eighth place due to decreasing trends in both incidence and mortality. In other countries, however, stomach cancer is still one of the most frequent cancer killers. For males in Japan, for example, the stomach cancer mortality rate is five times that for males in the United States and accounts for one-fourth of male cancer deaths. For females in Japan, the stomach cancer mortality rate is seven times the U.S. rate and accounts for nearly one-fourth of all female cancer deaths in Japan.

- ^a 1986 only
- ^b 1986–87 only
- ^c 1987 only
- ^d 1987–88 only

Rates are age-adjusted to the world standard

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Stomach, Males



Stomach, Females



Cancer Death Rates Among 50 Countries

Cervix Uteri and Other Uterus

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Female

Cancers of the uterine cervix and uterine corpus (endometrium) differ in histologic type and risk factors. Most countries distinguish cervix uteri from the rest of the uterus. The remainder of this category is cancer of the corpus uteri and uterus not otherwise specified. Many deaths are listed only as uterine cancer, with no specificity as to the part of the uterus. The highest mortality rates for cancer of the cervix uteri are in Mexico and Central and South America. Two-thirds of the countries have rates of less than 5 per 100,000. The United States, with death rates of 2.7 for both sites, ranks 37th for cancer of the cervix and 33rd for "other uterus." Incidence and mortality rates for cancer of the cervix uteri have been declining in the United States.

- ^a 1986 only
- ^b 1986–87 only
- ^c 1987 only
- ^d 1987–88 only

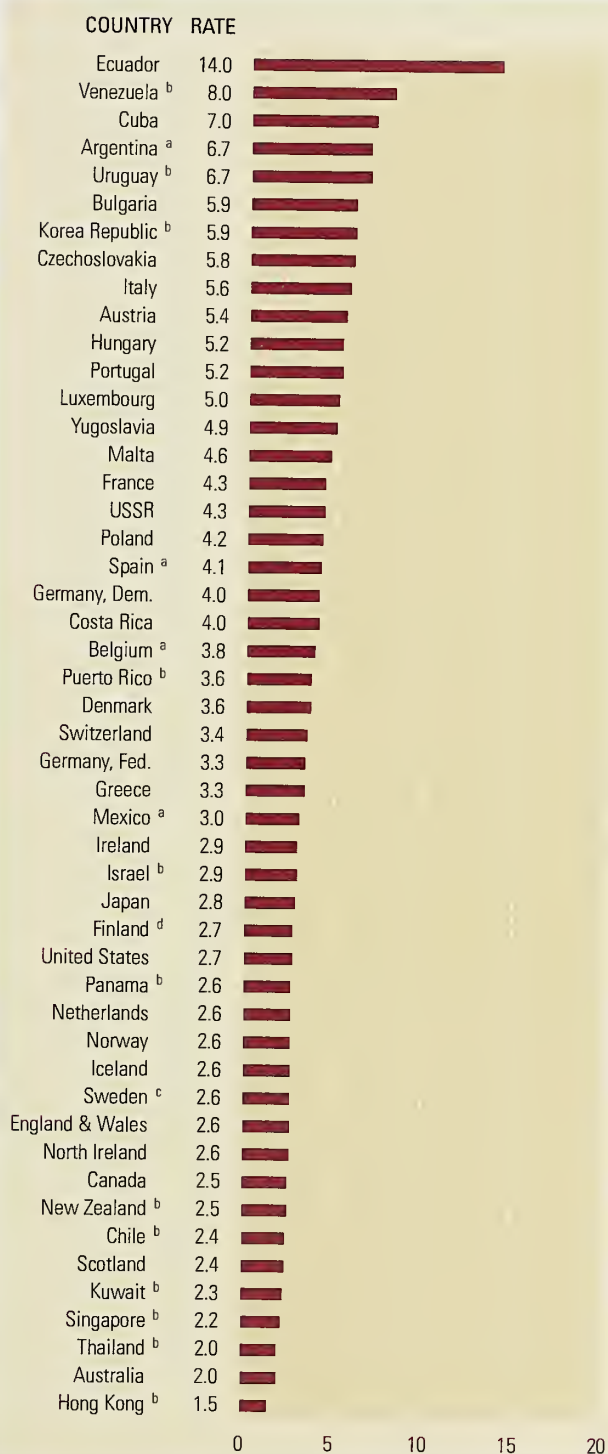
Rates are age-adjusted to the world standard.

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Cervix Uteri, Females



Other Uterus, Females



Cancer Death Rates Among 50 Countries

Oral Cavity

1986–88 Age-adjusted
Death Rates per
100,000 Population,
Male and Female

As they do for many other cancer sites, females have much lower death rates than males for cancer of the oral cavity and pharynx (mouth and throat). In all but three countries, the mortality rate for females is less than 2 per 100,000. Oral cavity cancer death rates for men range from a low of 0.9 per 100,000 in Ecuador to a high of 14.8 in Hong Kong. Oral cavity rates for China may be somewhat lower than they should be, because the Chinese report only nasopharynx for this site; i.e., they do not include other parts of the oral cavity and pharynx in this category.

- ^a 1986 only
- ^b 1986–87 only
- ^c 1987 only
- ^d 1987–88 only
- ^e Mortality rate includes nasopharynx only.

Rates are age-adjusted to the world standard

Source: World Health Organization data as adapted by the American Cancer Society, 1992

Oral Cavity, Males



Oral Cavity, Females



REFERENCES

- Boring CC, Squires TS, Tong T. Cancer Statistics, 1992. *Ca - A Cancer Journal for Clinicians* Vol 42: No. 1, January-February 1992.
- McKay FW, Hanson MR, Miller RW. Cancer Mortality in the United States: 1950-1977. *J Natl Cancer Ins Mono* 59: 1982. NIH Pub. No. 82-2435.
- Parkin DM, Muir CS, Whelan S, et al.: *Cancer Incidence in Five Continents, Vol. VI*. IARC Scientific Publications No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al. (eds.): *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*, National Cancer Institute. NIH Pub. No. 94-2789, Bethesda, MD, 1994.

R I S K S



Exposure to environmental pollutants is nearly unavoidable, but while the number of polluting substances in the general environment is large, their concentrations are generally low compared to exposures encountered in certain workplaces.

The effects of exposure to general pollutants in air and water are not clear, although some estimates cite pollution for causing from 1 to 5 percent of all cancer deaths (Doll and Peto, 1981).

Air Pollution

Pollutants in the urban air have long been suspect as causes of lung cancer (Blot and Fraumeni, 1992), but evaluation is difficult because of the problems of defining and measuring air pollution and of measuring effects of low-level exposures in large populations (National Research Council, 1979). Of special concern are products from the combustion of fossil fuels found principally in motor vehicle exhausts (especially diesel engines), residential and commercial space heating, oil and coal-fired power plants, and industrial emissions. Several studies have found a statistical link between measured levels of specific combustion products in urban air and lung cancer rates, but a major confounding factor appears to be differences in urban and rural cigarette smoking, with some effect from occupational hazards. Another approach has been to extrapolate from studies of workers heavily exposed to air pollutants found at lower levels in the environment. Using this technique, researchers have suggested that the causative effect of urban air pollution on lung cancer is about one-tenth the effect of smoking on men with average smoking habits (Doll, 1978). Some research suggests that the carcinogenic effects of smoking on the lung are enhanced in urban areas, indicating that pollutants in the urban atmosphere may increase the carcinogenic potency of tobacco smoke (Friberg and Cederlof, 1978).

Recent studies in areas of China with unusually high lung cancer rates provide some of the strongest evidence that specific air pollutants can increase lung cancer risk. In one investigation, women and men living in chimneyless houses heated by a local soft, smoking coal had especially high risk (Mumford et al., 1987). Indoor coal-burning devices that release smoke and fumes into the indoor environment contribute to high lung cancer rates in urban Shenyang and Harbin (Xu et al., 1989; Wu-Williams et al., 1990). In Shenyang, levels of some specific pollutants in indoor and outdoor environments exceeded recommended standards for U.S. cities by more than 60-fold.

Products of combustion are not the only carcinogenic air pollutants. Lung cancer occurs excessively in neighborhoods adjacent to arsenic-emitting smelters in the United States, Sweden, and China (Brown et al., 1984; Pershagen, 1986; Xu et al.,

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

1989). Asbestos bodies are present in the lungs of large segments of the urban population, although it is not directly established that lung cancer occurs excessively following low-dose, non-occupational exposures to asbestos (Churg and Warnock, 1979). Nevertheless, the well-known link between occupational exposure to asbestos and lung cancer has led to concern about airborne exposures to asbestos in consumer products, schools, office buildings, and other public places (Mossman et al., 1990).

Exposure to radioactive emissions from radon in uranium mines has been shown to be responsible for the increased risk of lung cancer among miners. Recent concern has focused on radon exposures in homes, particularly those that have been made air-tight by efficient insulation. Radon can enter the home from soil, water, or building materials. Scientists at the National Cancer Institute (Lubin and Boice, 1989) and the Environmental Protection Agency (EPA) (U.S. Environmental Protection Agency, 1992) have estimated that about 13,000 lung cancers a year may result from exposure to radon in the home environment. The Environmental Protection Agency has suggested that homes with indoor radon levels above 4 picocuries per liter be subject to modifications, although others recommend consideration of remediation only at levels of 5 to 10 picocuries per liter or higher.

Lowering indoor radon in this way would protect the persons at greatest risk. However, the total number of lung cancers that result from this exposure would likely be decreased only by a few percent, because such a large part of the U.S. population is exposed to lower levels of indoor radon (Lubin and Boice, 1989).

Cigarette smoking is a well-established cause of a number of cancers. Numerous studies have also shown a small, but measurable, increase in the risk of lung cancer among non-smoking spouses of smokers, presumably the result of their passive exposure to tobacco smoke in the home environment (National Research Council, 1986; International Agency for Research on Cancer, 1986; Environmental Protection Agency, 1992).

Water Pollution

Drinking water contains complex mixtures of known and suspected carcinogens, including asbestos, metals, radioactive substances, and industrial chemicals. In addition, the process of treating water may create small quantities of chemicals that have been linked to cancer in laboratory animals.

Chlorination byproducts, including chloroform, other trihalomethanes (or THMs), and other compounds, can be formed when chlorine used to purify drinking water reacts with organic compounds in water. Even at levels normally found in some chlorinated city water supplies with high levels of organic material, there is

Air and Water Pollutants

Air and Water Pollutants

suspicion that the byproducts may increase the risk of gastrointestinal and urinary tract cancers (Crump and Guess, 1982; Cauter et al., 1987). To reduce the levels of chlorination byproducts, water is often filtered to reduce the amount of chlorine needed for purification.

A few other industrial chemicals, known to cause cancer in humans, have been found occasionally in drinking water (National Research Council, 1977). Vinyl chloride, for example, may be introduced into drinking water from industrial plants or, in very small amounts, by seepage from polyvinyl chloride piping used in some water distribution systems. Benzene and bis(2-chloroethyl)ether are other carcinogens that are occasionally found in drinking water.

Nitrates themselves do not cause cancer, but they can combine in the body with certain amines to form nitrosamines, many of which are powerful carcinogens in animal models. In most circumstances, ingested nitrate comes primarily from food, but water can be the primary source of consumed nitrate in places where nitrate in drinking water is close to, or above, the maximum level set by the EPA. Nitrates are seldom eliminated by the water treatment process. The evidence linking nitrate to human cancer is weak. Some studies point to an association; others do not. Therefore, if there is a connection, the link is not likely to be strong (Fraser et al., 1980).

Asbestos fibers are widely distributed in water supplies in this country, with higher levels often found near cities and industrial centers. But studies have not shown consistently that asbestos in drinking water affects cancer risk (Working Group on Ingested Asbestos, 1987).

The trace metals arsenic, chromium, and nickel are found in drinking water in varying amounts. They may come from industrial plants and mines; by seepage from soil or piping; by mineralization from rocks; or from water treatment processes. High levels of arsenic in drinking water in Taiwan and some other countries have been linked with several types of cancer (bladder, kidney, lung, nasal cavity, and liver in both sexes, and prostate) (Chen and Wang, 1990; Wu et al., 1989). However, the levels of arsenic in almost all U.S. drinking waters are considered low enough not to constitute a public health threat.

Depending on local rock type and on the handling of radioactive compounds by nearby industries, hospitals, and nuclear power plants, radioactive substances may be found in the water supply. While the radioactive strontium and radium found in some waters can accumulate in bone tissue, the low cumulative dose from radium would result in so few fatal bone cancers that they would probably not be detected in epidemiologic studies.

Air and Water Pollutants

Naturally occurring radon gas is found dissolved in water in some parts of the United States. Ingestion of radon in water does not pose much of a direct hazard, because of its low concentration; but radon can be released into household air via showers, washing machines, and other water usage. In some cases, waterborne radon released into the air can contribute substantially to domestic airborne levels. Based on the results of studies of underground miners exposed to much higher levels of radon, elevated levels of radon in houses is suspected to contribute to lung cancer risk (Samet, 1989).

Water that percolates below the earth's surface, known as groundwater, is the source of spring and well water. Seepage of pesticides, industrial solvents, and other industrial chemicals such as polychlorinated biphenyls (PCBs) into the underground aquifers (rock formations that hold water) causes further contamination of the groundwater supply.

Burying hazardous wastes on land is the most common method of disposal in this country because it is inexpensive. Disposal sites can leak, however, and contamination of groundwater near the older sites has been documented in many locations. Therefore, the EPA has instituted more rigorous guidelines regulating hazardous waste disposal.

Under EPA guidelines, the major U.S. water supplies are monitored regularly for a number of carcinogens. National Cancer Institute scientists have been studying the possible link between cancer and drinking water quality (Cantor, 1990). The available evidence suggests that the cancer risk posed by contaminants in our drinking water is relatively small.

REFERENCES

- Blot WJ and Fraumeni JF Jr: Lung and pleural cancer. In *Cancer Epidemiology and Prevention*, 2nd ed. (Schottenfeld D and Fraumeni JF Jr, eds). Philadelphia: W.B. Saunders, in press.
- Brown LM, Pottern LM, and Blot WJ: Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ Res* 34:250-261, 1984.
- Cantor KP: Epidemiologic studies and risk assessment of volatile organic compounds in drinking water. pp. 165-184. In *Significance and Treatment of Volatile Organic Compounds in Water Supplies* (Ram NM, Christman RE, Cantor KP, et al., eds.). Lewis Publishers, 1990.
- Cantor KP, Hoover R, Hartge P, et al.: Bladder cancer, drinking water source, and tap water consumption: a case-control study. *J Natl Cancer Inst* 79:1269-1279, 1987.
- Chen CJ and Wang CJ: Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res* 50:5470-5474, 1990.
- Churg AM and Warnock ML: Numbers of asbestos bodies in urban patients with lung cancer and gastrointestinal cancer and in matched controls. *Chest* 76:143-149, 1979.
- Crump KS and Guess HA: Drinking water and cancer: Review of recent epidemiological findings and assessment of risks. *Annu Rev Public Health* 3:339-357, 1982.
- Doll R: Atmospheric pollution and lung cancer. *Environ Health Perspect* 22:23-31, 1978.
- Doll R and Peto R: The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66:1191-1308, 1981.
- Environmental Protection Agency: Respiratory Health Effects of Passive Smoking: Lung cancer and other disorders. Washington, DC: EPA, 1992.
- Fraser P, Chilvers C, Beral V, et al.: Nitrate and human cancer: a review of the evidence. *Int J Epidemiol* 9:3-11, 1980.
- Friberg L and Cederlof R: Late effects of air pollution with special reference to lung cancer. *Environ Health Perspect* 22:45-66, 1978.
- International Agency for Research on Cancer: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking. Lyon, France: IARC, vol. 38, 1986.
- Lubin JH, Boice JD Jr: Estimating Rn-induced lung cancer in the United States. *Health Phys* 57:117-127, 1989.
- Mirvish SS, Grandjean AC and Moller H: N-nitrosoproline excretion by rural Nebraskans drinking water of varied nitrate content. *Cancer Epidemiol Biomarkers Prev* 1:155-61, 1992.
- Mossman BT, Bignon J, Corn M, et al.: Asbestos: Scientific developments and implications for public policy. *Science* 247:294-301, 1990.
- Mumford JL, He XZ, Chapman RS, et al.: Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 235:217-220, 1987.
- National Research Council: Board on Environmental Studies and Toxicology Committee on Passive Smoking: Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, DC: National Academy Press, 1986.
- National Research Council: Committee on Medical and Biologic Effects of Environmental Pollutants: Airborne Particles. Baltimore: University Park Press, 1979.
- National Research Council: Drinking Water and Health. Vol. 1, Washington, DC: National Academy of Sciences, 1977.
- Pershagen G: Lung cancer mortality among men living near an arsenic-emitting smelter. *Am J Epidemiol* 122:684-694, 1985.
- Samet JM: Radon and lung cancer. *J Natl Cancer Inst* 81:745-757, 1989.
- U.S. Environmental Protection Agency, Office of Radiation Programs: Technical Support Document for the 1992 Citizen's Guide to Radon. Washington, DC: Government Printing Office, 1992.
- Working Group on Ingested Asbestos: DHHS report on cancer risks associated with ingestion of asbestos. *Environ Health Perspect* 72:253-265, 1987.
- Wu MM, Kuo TL, Hwang YH, et al.: Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 130:1123-1132, 1989.
- Wu-Williams AH, Dai XD, Blot WJ, et al.: Lung cancer among women in northeast China. *Br J Cancer* 62:982-987, 1990.
- Xu ZY, Blot WJ, Xiao HP, et al.: Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst* 81:1800-1806, 1989.

Alcohol

William J. Blot, Ph.D.*

Epidemiologic investigations have provided definitive evidence that the drinking of alcoholic beverages can induce cancer in humans (IARC, 1988). Risks of all cancers combined rise as the level of intake increases; the largest study shows a detectable increase in risk following consumption of three alcoholic drinks per day which rises to a 60 percent excess with six or more drinks per day (Boffetta and Garfinkel, 1990).

Risks due to alcohol vary considerably by type of cancer. The strongest associations are with oral, pharyngeal, esophageal, and laryngeal cancer. Cigarette smoking, which is also a major determinant of each of these cancers, tends to combine synergistically with alcohol in enhancing risk.

In the mid-1980s, a large U.S. case-control study of oral and pharyngeal cancer provided the most detailed measurements available of the effects of drinking (and its interaction with smoking) on these cancers (Blot et al. 1988). Within each category of smoking, risks of oral and pharyngeal cancer tended to increase as alcohol intake increased. People who consumed an average of more than four drinks per day incurred a nine-fold increase in risk of oral and pharyngeal cancer, while there was about a four-fold increase in risk associated with smoking two or more packs of cigarettes per day. Heavy drinkers who also were heavy smokers experienced a greater than 36-fold excess compared to abstainers from both products, suggesting that much of the effect of alcohol on these cancers is enhanced by the effect of tobacco, and that reduction in either one of the products will substantially reduce risk. Indeed, it is estimated that 75 percent of all oral and pharyngeal cancers in the United States are due to drinking and smoking. But, even among nonsmokers, risks of oral and pharyngeal cancers rise with increasing intake of alcohol. While heavy consumption of all types of alcoholic beverages seems to increase risk of these cancers, there is some suggestion that the association is more pronounced for hard liquor and beer than for wine.

Esophageal cancer is also induced by the combined effects of alcohol and tobacco, although alcohol alone can increase risk of this cancer in nonsmokers as well (IARC, 1988). In some areas of the world, particular alcoholic beverages have been associated with exceptionally high rates of esophageal cancer. For example, in the Calvados region of northern France, very high rates of esophageal cancer have been linked to consumption of local apple brandies (Tuyns et al., 1979). Home-brewed rum has been associated with high rates of esophageal (and oral) cancers in Puerto Rico (Martinez, 1969), and cachaca (another distilled spirit of sugar cane) has been implicated in the elevated risk of esophageal cancer in Brazil (Victora, 1987). In coastal areas of South Carolina, which has led the nation in death rates from esophageal cancer for several decades, nearly 90 percent of black male patients with this cancer reported they were regular consumers of moonshine whiskeys (Brown et al., 1988).

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda,
Maryland

Alcohol

Drinkers run a higher relative risk for cancers of the extrinsic larynx, which comes in contact with alcohol during drinking, than the intrinsic larynx (Elwood et al., 1984), suggesting that alcohol may act through topical exposure to increase risk of upper aerodigestive tract cancers. A recent report has also associated long-term use of mouthwashes high in alcohol content with increased risk of oral cancer, also suggesting an effect of topical rather than systemic exposure since mouthwashes are seldom swallowed (Winn et al., 1991).

The observations of increased risks of oral, pharyngeal, esophageal, and laryngeal cancer associated with nearly all types of alcoholic beverages implicate a dominant effect for common ingredients, particularly ethanol (Blot, 1992). Although ethanol itself and alcoholic beverages have generally not induced cancer in experimental animals, the epidemiologic evidence is sufficient to establish carcinogenicity (IARC, 1988). The variation in risk by type of beverage, however, suggests that substances other than the alcohol may in some instances contribute to the risk.

Alcohol is also a recognized cause of liver cancer. Deaths from this cancer are increased about 50 percent among alcoholics and other heavy drinkers (IARC, 1988). By altering liver function and the liver's ability to metabolize some substances into compounds that may be carcinogenic or to deactivate certain existing carcinogens, alcohol's effects on the liver may influence not only liver cancer but cancers at other sites as well.

More than 50 epidemiologic studies in the past decade have found small to modest increases in risks of breast cancer associated with drinking alcoholic beverages (Schatzkin et al., 1994). Two large cohort studies involving nearly 600,000 women detected a 20 to 30 percent excess of breast cancer associated with consumption of about one drink per day, with 60 to 70 percent excesses among heavy drinkers (Colditz et al., 1990; Garfinkel et al., 1988). Further research is needed to clarify whether the association between alcohol and breast cancer is causal in nature.

Several epidemiologic studies suggest that alcohol may induce colorectal cancers, particularly rectal cancer, but the findings are not totally consistent. The overall evidence suggests that alcohol is not causally related to cancers of the stomach, pancreas, lung, bladder, and other tumors not mentioned earlier (IARC, 1988).

Moderation of intake is the key to prevention of alcohol-induced cancer. Because many of the cancers induced by alcohol result from heavy consumption, reducing levels of consumption will considerably lessen the risk. Because of the interaction of alcohol and tobacco, smoking cessation will also reduce the effect of alcohol on oral, pharyngeal, esophageal, and laryngeal cancers.

REFERENCES

- Blot WJ: Alcohol and cancer. *Cancer Res* 1:52 (7 Suppl):2119s-2123s, 1992.
- Blot WJ, McLaughlin JK, Winn DM, et al.: Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 48:3282-3287, 1988.
- Boffetta P and Garfinkel L: Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiol* 1:342-348, 1990.
- Brown LM, Blot WJ, Schuman SH, et al.: Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *J Natl Cancer Inst* 80:1620-1625, 1988.
- Colditz GA: A prospective assessment of moderate alcohol intake and major chronic diseases. *Ann Epidemiol* 1:167-177, 1990.
- Elwood JM, Pearson JC, Skippen DH, et al.: Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx, and larynx. *Int J Cancer* 34:603-612, 1984.
- Garfinkel L, Boffetta P and Stellman SD: Alcohol and breast cancer: a cohort study. *Prev Med* 17:686-693, 1988.
- International Agency for Research on Cancer: Alcohol Drinking. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, vol 44. IARC, Lyon, 1988.
- Longnecker MP, Berlin JA, Orza MJ, et al.: A meta-analysis of alcohol consumption in relation to risk of breast cancer. *JAMA* 260:652-656, 1988.
- Martinez I: Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst* 42:1069-1094, 1969.
- Tuyns AG, Pequignot G and Abbatucci JS: Esophageal cancer and alcohol consumption: importance of type of beverage. *Int J Cancer* 23:443-447, 1979.
- Victora CG, Munoz N, Day NE, et al.: Hot beverages and esophageal cancer in southern Brazil: a case-control study. *Int J Cancer* 39:710-716, 1987.
- Winn DM, Blot WJ, McLaughlin JK, et al.: Mouthwash use and oral conditions in the risk of oral and pharyngeal cancer. *Cancer Res* 51:3044-3047, 1991.

Anticancer Drugs

Margaret A. Tucker, M.D.*

In the past several decades, anticancer drugs have prolonged the lives of many thousands of cancer patients and have cured a substantial number of them. Unfortunately, some of these patients have developed second cancers as a consequence of the treatment for the first cancer.

The class of chemotherapy drugs which has been most closely linked to the development of second cancers are the alkylating agents, which work by inserting foreign molecules into the genetic material of dividing cancer cells. These foreign molecules kill cells by disrupting their normal function and by preventing their further growth and multiplication. However, these chemotherapy drugs not only affect the cancer cells but also disrupt normal cell growth in progress—in the lining of the gastrointestinal tract, blood cells, hair, nails, and any other part of the body where cells happen to be growing when the drugs are given. In addition to killing cells, the alkylating agents can produce mutations not unlike those produced by radiation. These mutations occasionally lead to cancer.

Excessive occurrence of a relatively rare type of acute nonlymphocytic leukemia (ANL) has been reported following the treatment of a variety of first cancers with alkylating agents. A number of characteristics, including its short latency period, distinguish it from spontaneous ANL: cases appear as early as two years following initial therapy and peak around five years post-treatment, and it is exceedingly resistant to treatment. Excesses of this leukemia appear after treatment of childhood cancers (Tucker et al., 1987b), Hodgkin's disease (Kaldor et al., 1990; Tucker et al., 1988; Valgussa, 1990; Valgussa et al., 1986; Van Leeuwen, 1989), non-Hodgkin's lymphoma (Greene et al., 1983), and cancers of the ovary (Greene et al., 1982; Greene et al., 1986), breast (Curtis et al., 1990; Fisher et al., 1985), lung (Chak et al., 1984; Pedersen-Bjergaard et al., 1985; Ratain et al., 1987), brain (Greene et al., 1985), and gastrointestinal tract (Boice et al., 1980; Boice et al., 1983). Characteristic cytogenetic changes are often found in chromosomes 5 and 7 (LeBeau et al., 1986). In general, the overwhelming risk factor for the development of these secondary leukemias is chemotherapy with alkylating agents. For example, a long-term follow-up study of patients treated for Hodgkin's disease found a relative risk of 115; i.e., the occurrence was 115 times as high as what would be expected in the general population. The risk plateaus about ten years after treatment and then decreases (Tucker et al., 1988). In another study, women receiving chemotherapy for ovarian cancer had a relative risk of leukemia of 93, while no cases occurred among those treated with surgery alone. The risk appears to peak at around six years (Greene et al., 1986).

* From the Genetic Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Anticancer Drugs

A number of studies investigating the relationship of the drugs to the development of leukemia have been published. In every study that has adequately evaluated dose, the risk of leukemia rises with increasing total amount of alkylating agents. Some studies have also demonstrated that alkylating agents vary in their propensity to cause leukemia. The risks of leukemia following treatment with cyclophosphamide, a commonly used alkylating agent, are much lower than the risks following treatment with melphalan or chlorambucil (Greene et al., 1982; Greene et al., 1986).

Although radiation treatments alone can cause leukemia, whatever additional risks they pose are difficult to measure in the presence of alkylating agents, since the risks associated with these agents are so much higher (Tucker et al., 1987b; Kaldor et al., 1990).

Concerns about the ability of other types of chemotherapeutic agents to cause cancers have been raised, and are currently being evaluated (Pui et al, 1990). Also under investigation is the role of chemotherapy in the development of solid tumors. Through the first ten years after treatment, leukemia predominates as the secondary cancer and then gives way to solid tumors (Tucker et al., 1988).

There are now reliable data showing that the risk of bladder cancer is elevated after treatment with cyclophosphamide (Pedersen-Bjergaard et al., 1988), and some preliminary evidence that the risk of bone sarcomas may be elevated after treatment of childhood cancers with alkylating agents (Tucker et al., 1987a). All of these long-term effects are being monitored closely and are affecting the design of future clinical trials. It is essential to recognize that the evaluation of late effects of treatment is a reflection of success in treating the first tumor; individuals are now living long periods after the first cancer. Many of these effects occur five or more years after the first and, in the case of solid tumors, often over 15 years. New clinical trials are incorporating the information on late effects to try to decrease the toxicity of treatments without sacrificing any of the efficacy and success of current treatment regimens.

REFERENCES

- Boice JD Jr, Greene MH, Keehn RJ, et al.: Late effects of low-dose adjuvant chemotherapy in colorectal cancer. *J Natl Cancer Inst* 64:501-511, 1980.
- Boice JD Jr, Greene MH, Killen JY, et al.: Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). *N Engl J Med* 309:1079-1084, 1983.
- Chak LY, Sikic BI, Tucker MA, et al.: Increased incidence of acute nonlymphocytic leukemia following therapy in patients with small cell carcinoma of the lung. *J Clin Oncol* 2:385-390, 1984.
- Curtis RE, Boice JD Jr, Moloney WC, et al.: Leukemia following chemotherapy for breast cancer. *Cancer Res* 50:2741-2746, 1990.
- Fisher B, Rockette H, Fisher E, et al.: Leukemia in breast cancer patients following adjuvant chemotherapy or post-operative radiation: the NSABP experience. *J Clin Oncol* 3:1640-1658, 1985.
- Greene MH, Boice JD Jr, Greer GE, et al.: Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. *N Engl J Med* 307:1416-1421, 1982.
- Greene MH, Boice JD Jr, and Strike TA: Carmustine as a cause of acute nonlymphocytic leukemia. *N Engl J Med* 313:579, 1985.
- Greene MH, Harris EL, Gershenson DM, et al.: Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med* 105:360-367, 1986.
- Greene MH, Young RC, Merrill JR, et al.: Evidence of a treatment dose response in acute nonlymphocytic leukemias which occur after therapy of non-Hodgkin's lymphoma. *Cancer Res* 43:1891-1898, 1983.
- Kaldor JM, Day NE, Clarke EA, et al.: Leukemia following Hodgkin's disease. *N Engl J Med* 322:7-13, 1990.
- LeBeau M, Albain KS, Larson RA, et al.: Clinical and cytogenetic correlation in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. *J Clin Oncol* 4:325-345, 1986.
- Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al.: Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med* 318:1028-32, 1988.
- Pedersen-Bjergaard JP, Osterlind K, Hansen M, et al.: Acute nonlymphocytic leukemia, preleukemia, and solid tumors following intensive chemotherapy of small-cell carcinoma of the lung. *Blood* 66:1393-1397, 1985.
- Pui C-H, Behm FG, Raimondi SC, et al.: Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. *N Engl J Med* 321:136-142, 1990.
- Ratain MJ, Kaminer LS, Bitran JD, et al.: Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung. *Blood* 70:1112-1117, 1987.
- Tucker MA, Coleman CN, Cox RS, et al.: Risk of second malignancies following Hodgkin's disease after 15 years. *N Engl J Med* 318:76-81, 1988.
- Tucker MA, D'Angio GJ, Boice JD Jr, et al.: Bone sarcoma linked to radiotherapy and chemotherapy in children. *N Engl J Med* 317:588-593, 1987a.
- Tucker MA, Meadows AT, Boice JD Jr, et al.: Leukemia after therapy with alkylating agents for childhood cancer. *J Natl Cancer Inst* 78:159-161, 1987b.
- Valagussa P: Second malignancies: the experience of the Milan Cancer Institute. *J Cancer Res Clin Oncol* 116 [Suppl]:982, 1990.
- Valagussa P, Santoro A, Fossati-Bellani F, et al.: Second acute leukemia and other malignancies following treatment for Hodgkin's disease. *J Clin Oncol* 4:830-837, 1986.
- Van Leeuwen FE, Somers R, Taal BG, et al.: Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. *J Clin Oncol* 7:1046-1058, 1989.

Tobacco use, particularly in the form of cigarette smoking, is the single most preventable cause of excess mortality in the United States. Each year, more people die prematurely from smoking than die from automobile accidents, drug abuse, AIDS, and alcohol combined (USDHS, 1989). An estimated 434,000 Americans died as a result of their smoking last year alone. Former Surgeon General C. Everett Koop has called cigarette smoking "...the chief, single, avoidable cause of death in our society and the most important public health issue of our time." (USDHS, 1982)

A series of authoritative reports by the U.S. Public Health Service and other international scientific organizations has conclusively documented a causal relationship between cigarette smoking and cancer of at least eight major sites (Shopland et al., 1991). These reports have uniformly identified smoking as a major cause of cancers of the lung, larynx, oral cavity, and esophagus—that is, cigarette smoking is responsible for a majority of the cases and deaths from cancer of these sites. These reports have also demonstrated that smoking substantially elevates the death rates for cancers of the bladder, kidney, and pancreas in both men and women, and, possibly, cervical cancer in women. A number of published reports have suggested an association between smoking and other cancers, including cancer of the stomach, liver, prostate, colon, and rectum.

Recent evidence published by investigators at the National Cancer Institute and the American Cancer Society (Shopland et al., 1991) conclusively demonstrates that the cancer risks among current cigarette smokers are greater today than at the time of the first Surgeon General's report in the early 1960s. Table 1 reports the relative risks of early cancer mortality for the eight major smoking-associated cancer sites among smoking men and women compared to nonsmokers. These data are taken from the large American Cancer Society Cancer Prevention Study II of more than 1.2 million individuals (685,748 women and 521,555 men) followed prospectively since 1982 (Shopland et al., 1991). This study clearly shows that, for each site, mortality risks among current smokers are higher than those among nonsmokers. Mortality risks in former smokers are lower than in those who continue to smoke, but higher than in those subjects who had never smoked.

The risk of developing any of the smoking-related cancers is dose-related; that is, the more cigarettes consumed daily, the younger the age at which one initiates smoking, and the more years one smokes, the greater the risk.

Among male cigarette smokers, the risk of lung cancer is more than 2,000 percent higher than among male nonsmokers; for women, the risks were approximately 1,200 percent greater. Lung cancer is the single largest cause of cancer mortality among both men and women and accounts for more than one in every four cancer deaths nationally in the U.S.

Cigarette Smoking as a Cause of Cancer

Donald R. Shopland*

* From the Smoking and Tobacco Control Program, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

Cigarette Smoking as a Cause of Cancer

In addition to cigarette smoking as a cause of cancer in smokers, environmental tobacco smoke (ETS) (also called involuntary or passive smoking) is now recognized as a significant cause of lung cancer in nonsmokers (National Research Council, 1986; DHS, 1987; EPA, 1993). Nonsmokers who live or work with smokers experience a 30 to 50 percent elevated risk for lung cancer. An estimated 3,000 to 6,000 nonsmoker lung cancer deaths annually are attributed to ETS (EPA, 1993). While the number of ETS related lung cancer deaths may seem small when compared to the number attributed to active smoking, the number is actually quite large when compared to other indoor and outdoor environmental pollutants (Table 2), many of which are regulated by the U.S. Environmental Protection Agency. By way of comparison, two British scientists have estimated that exposure to asbestos fibers among people who live or work in asbestos-containing buildings carries an annual risk of lung cancer of less than 1 in 1 million (Doll and Peto, 1986). Notwithstanding this small risk, great efforts are made to remove asbestos from work sites, schools, and other public buildings because the risks are deemed to be unacceptable. Yet, according to these same investigators, the relative risk for lung cancer due to ETS "is more than 100 times higher than the estimated effects of 20 years' exposure to the amount of chrysotile asbestos normally found in asbestos-containing buildings." (Peto and Doll, 1986)

Smokeless tobacco users are at increased risk for cancers of the oral cavity, particularly cancers of the cheek and gum (DHS, 1986), and evidence also suggests an association between use of smokeless tobacco and cancers of the larynx and esophagus.

Pipe and cigar smokers experience substantially elevated risks for cancers of the oral cavity, larynx, pharynx, and esophagus, which equal and often exceed the risks observed in regular cigarette smokers (USDHEW, 1979). Pipe and cigar smokers experience a slightly increased risk for lung cancer; however, among pipe and cigar smokers who inhale, the risk of lung cancer is on the same order of magnitude found in cigarette smokers.

The total magnitude of the cancer burden caused by smoking is staggering. Of the 514,000 cancer deaths expected to occur this year in the United States, slightly over 164,000, or nearly one-third, are directly linked to cigarette smoking (Table 1). An additional 14,000 deaths can reasonably be attributed to pipe and cigar smoking among men. In all, it is estimated that cigarette smoking causes approximately 23 percent of all cancer deaths in women, but the combination of pipe, cigar, and cigarette smoking is responsible for 42 percent of all male cancer deaths (Shopland et al., 1991). If cancer deaths associated with tobacco use were excluded from national cancer mortality figures, we would be witnessing a substantial downturn in both overall cancer deaths and rates.

TABLE 1
1994 U.S. Cancer Deaths Caused by Cigarette Smoking

Site and ICD Disease Category	1994 Cancer Deaths Expected	Smoking Attributable Risk %	Estimated Deaths due To Smoking
MALES			
140-149 Oral	5,150	90.0	4,635
150 Esophagus	7,800	76.7	5,983
157 Pancreas	12,400	25.6	3,174
161 Larynx	3,000	79.3	2,379
162 Lung	94,000	89.2	83,848
188 Bladder	7,000	43.1	3,017
189 Kidney	6,800	44.6	3,033
<i>Total Male Cancer Deaths Expected</i>	<i>283,000</i>		<i>106,069 (37.5%)</i>
FEMALES			
140-149 Oral	2,775	58.5	1,624
150 Esophagus	2,600	71.6	1,862
157 Pancreas	13,500	31.2	4,212
161 Larynx	800	86.9	695
162 Lung	59,000	78.5	46,315
180 Cervix	4,600	30.8	1,417
188 Bladder	3,600	34.3	1,235
189 Kidney	4,500	15.3	689
<i>Total Female Cancer Deaths Expected</i>	<i>255,000</i>		<i>58,049 (22.8%)</i>
Total male and female cancer deaths expected in 1994	538,000		
Total excess deaths due to cigarette smoking	164,118		
Percent attributed to cigarette smoking	30.5%		

Source: Based on data in Shopland et al., 1991.

Cigarette Smoking as a Cause of Cancer

Cigarette Smoking as a Cause of Cancer

In short, all forms of tobacco use are hazardous, but the hazards are magnified when smoke from the tobacco is inhaled. Furthermore, the nicotine in tobacco is addictive, which makes it extremely difficult for most users to stop the behavior once it has been adopted as part of their lifestyle (DHS, 1988).

What's in Cigarette Smoke to Cause so Many Diseases?

Tobacco smoke contains literally thousands of chemical agents, including 60 constituents which are known carcinogens, cocarcinogens, or tumor promoters (DHEW, 1979). Because the average smoker consumes about 30 cigarettes daily, the smoker is being subjected to a constant barrage of hazardous agents. After many years of smoking, it is not surprising that smokers die many years prematurely from cancer, heart disease, emphysema, bronchitis, and other chronic and debilitating diseases at rates substantially higher than persons who never smoke.

The Health Benefits of Quitting Smoking

Quitting smoking greatly reduces the risks for all these diseases (DHHS, 1990). For example, within a year of quitting, a former smoker's risk of heart disease is reduced by nearly 50 percent compared to someone who continues to smoke. Unfortunately, the risks for lung cancer do not decrease as rapidly, but the sooner one quits smoking, the quicker one begins to benefit (Table 3). Usually, after 10 to 15 years off cigarettes, most former smokers' health status is not significantly different from that of a lifelong nonsmoker. Any residual risk following cessation is strongly dependent on total previous exposure to cigarette smoke, length of time off cigarettes, and the health status of the individual at the time of cessation (Shopland, 1990).

TABLE 2

Comparison of Estimated Annual Cancer Deaths Expected From Various Airborne Carcinogens

Indoor Pollutant	Cancer Deaths
ETS	3,000 – 6,000
Radon (Nonsmokers only)	3,000
Asbestos*	4,280
Outdoor Pollutant	
Asbestos	15
Vinyl Chloride	<27
Benzene	<8
Arsenic	<5
Coke Oven Emissions	<15
Airborne Radionuclides	<17

* Expected deaths over next 130 years.

Source: Repace et al., 1985 and U.S. Environmental Protection Agency, 1993.

TABLE 3

Effect of Quitting Smoking on Lung Cancer Risk Among Male and Female Former Smokers, by Length of Time Off Cigarettes and Number of Cigarettes Smoked Daily

MALES		
	1–20 Cig/day	>21 Cig/day
Current Smokers	18.8	26.9
Former Smokers (year since stopped)		
<1	26.7	50.7
1–2	22.4	33.2
3–5	16.5	20.9
6–10	8.7	15.0
11–15	6.0	12.6
>16	3.1	5.5
FEMALES		
	1–19 Cig/day	>20 Cig/day
Current Smokers	7.3	16.3
Former smokers (year since stopped)		
<1	7.9	34.3
1–2	9.1	19.5
3–5	2.9	14.6
6–10	1.0	9.1
11–15	1.5	5.9
>16	1.4	2.6

Source: Based on data in Shopland et al., 1991.

Cigarette Smoking as a Cause of Cancer

REFERENCES

- Doll R, Peto J: Asbestos: Effects on Health of Exposure to Asbestos. London, HMSO, 1985.
- National Research Council: Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects. Washington, DC: National Academy Press, 1986.
- Peto J, Doll R: Passive smoking. *Brit J Ca* 1986; 54:381-383.
- Repace JL and Lowery AH: A quantitative estimate of non-smoker's lung cancer risk from passive smoking. *Environmental International* 11: 3-22, 1985.
- Shopland, DR: Changes in tobacco consumption and lung cancer risk: Evidence from studies of individuals. In *Evaluating effectiveness of primary prevention for cancer* (Hakam M, Beral V, Cullen J, et al., eds.) IARC Scientific Publication No. 103, 1990.
- Shopland, DR, Eyre HJ and Pechacek TF: Smoking-attributable mortality in 1991. Is lung cancer now the leading cause of death among smokers in the United States? *J Natl Cancer Inst* 83(16):1142-1148, 1991.
- U.S. Department of Health, Education and Welfare: Other forms of tobacco use. Chapter 13. In *Smoking and Health. A Report of the Surgeon General*. DHEW Pub. (PHS) 79-50066. Washington, DC, 1979.
- U.S. Department of Health and Human Services: The health benefits of smoking cessation. A Report of the Surgeon General, 1990. DHHS Pub. No. (CDC) 90-8416. Washington, DC, 1990.
- U.S. Department of Health and Human Services: The health consequences of involuntary smoking. A Report of the Surgeon General, 1986. DHHS Publ. No. (PHS) 87-8398. Washington, DC, 1987.
- U.S. Department of Health and Human Services: The health consequences of smoking: Cancer. A Report of the Surgeon General. DHHS Pub. No. (PHS) 82-50179. Washington, DC, 1982.
- U.S. Department of Health and Human Services: The health consequences of smoking: Nicotine addiction. A Report of the Surgeon General, 1988. DHHS Pub. No. (CDC) 88-8406. Washington, DC, 1988.
- U.S. Department of Health and Human Services: The health consequences of using smokeless tobacco. A Report of the Advisory Committee to the Surgeon General. DHHS Pub. No. (NHI) 86-2874. Washington, DC, 1986.
- U.S. Department of Health and Human Services: Reducing the health consequences of smoking—25 years of progress. A Report of the Surgeon General, 1989. DHHS Pub. No. (CDC) 89-8411. Washington, DC, 1989.
- U.S. Environmental Protection Agency. Respiratory health effects of passive smoking: Lung cancer and other disorders. The Report of the U.S. Environmental Protection Agency. Smoking and Tobacco Control Monograph no. 1. NHI Pub. No. 93-3605. Bethesda, MD, 1993.

As scientific research progresses, the evidence that dietary patterns, foods, nutrients, and other dietary constituents are closely associated with the risk for several types of cancer becomes more compelling. And while it is not yet possible to provide quantitative estimates of the overall risks, it has been estimated that 35 percent of cancer deaths may be related to dietary factors (Doll and Peto, 1981). The recommendations for dietary change currently before the American public are based on years of scientific research and offer potential for an effective public health approach to cancer prevention. Currently available research shows that diets low in fat and high in fiber, fruits, vegetables, and grain products are associated with reduced risks for many cancers

Dietary Fats

Diets high in fat have been linked to increased risk of various cancers, particularly breast, colon, prostate, and possibly pancreas, ovary, and endometrium (USDHHS, 1988; National Research Council, 1989). Studies of populations in countries consuming high-fat diets compared to low-fat diets have consistently shown higher incidence and mortality rates for breast, colon, and prostate cancer. There is substantial, but not conclusive, evidence that the international association between fat intake and the risk of breast and colon cancer is much stronger for total fat intake compared to the specific type of fat, i.e., saturated, monounsaturated, or polyunsaturated fat (Hursting et al., 1990). However, a combined analysis of 12 case-control studies showed a significant positive association between breast cancer risk and saturated fat intake in postmenopausal women (Howe et al., 1990). Recent studies in the same population of U.S. women reported that increased intakes of total saturated and monounsaturated fats were associated with increased colon cancer but not breast cancer (Willett et al., 1990, 1992).

Fat consumption in the United States is much higher than that needed to meet the physiological needs for energy and essential fatty acids. The average U.S. diet is estimated to contain approximately 37 percent of calories from fat. Dietary recommendations are to decrease total fat intake to 30 percent of calories. The major sources of fat in the American diet are added fats and oils used as spreads, cooking fats, and salad oils as well as the fat in meats and whole milk dairy products.

Because dietary fat intake is highly correlated with calorie intake, the question has been raised as to whether fat intake or calorie intake is the major dietary factor affecting cancer risk. However, the few studies that have addressed the relative importance of fat intake versus calorie intake suggest that both fat and calorie intake have independent effects. Dietary fat is the most concentrated source of energy of all the nutrients and supplies nine calories per gram compared to four calories per gram from either carbohydrate or protein. In general, a reduction in dietary fat intake is accompanied by a decrease in total calorie intake and body weight (Boyd et al., 1990; Henderson et al., 1990).

Diet and Cancer Risk

Carolyn Clifford, Ph.D.^a,
Rachel Ballard-Barbash, M.D.^b,
Elaine Lanza, Ph.D.^c, and
Gladys Block, Ph.D.^d

^a From the Diet and Cancer Branch,
Division of Cancer Prevention and
Control, National Cancer Institute,
Bethesda, Maryland

^b From the Applied Research Branch,
Division of Cancer Prevention and
Control, National Cancer Institute,
Bethesda, Maryland

^c From the Cancer Prevention Studies
Branch, Division of Cancer
Prevention and Control, National
Cancer Institute, Bethesda,
Maryland

^d From the Department of Public
Health Nutrition, University of
California, Berkeley, California

Diet and Cancer Risk

Dietary Fiber

Dietary fiber falls into two categories, water-soluble fiber and water-insoluble fiber, and is generally defined as those components of food plants resistant to the enzymes produced by the human digestive tract.

Increasing evidence suggests that diets high in fiber-containing foods are associated with a reduced risk for cancer, especially cancer of the colon (Trock et al., 1990). A few studies have also shown a reduced risk for cancers of the breast, rectum, oral cavity, pharynx, stomach, and other sites with diets rich in fruits, vegetables and grain products (Lanza et al., 1992). Because these foods contain other nutrients as well as fiber, and are usually lower in fat, it has not been possible to determine whether the protective effect is attributable to dietary fiber.

Fruits and Vegetables

Populations consuming diets high in fruits and vegetables tend to have a lower cancer risk. Fruits, vegetables, and grains contain a number of nutrients, including carotenoids, vitamin A, and vitamin C. The cancers for which there is evidence of a protective effect include those of the lung, colon and rectum, breast, oral cavity, esophagus, stomach, pancreas, uterine cervix, and ovary. For most cancer sites, especially epithelial cancers of the respiratory and digestive tracts, persons with low fruit and vegetable intake had about twice the risk of cancer as those with high intake (Block et al., 1992).

Carotenoids and Vitamin A

Numerous studies have found evidence that carotenoids reduce the risk of some cancers. The evidence is particularly strong for lung cancer (Ziegler, 1989), even after taking smoking into account. Every study that examined the role of carotene-rich foods found reduced lung cancer risk with higher intake, and about 20 of 25 studies yielded statistically significant results. Five of six studies of blood carotenoids found that persons with higher levels had reduced risk. There is no question that smoking is the strongest risk factor, and quitting smoking is the most important step to reduce risk. It appears, however, that there may be additional benefit to increasing the consumption of foods containing carotenoids.

Carotenoids are found in dark yellow/orange vegetables and fruits such as carrots, sweet potatoes, and cantaloupe and in deep green leafy vegetables such as broccoli, spinach, and collard greens. There are many different carotenoids in such foods, including beta-carotene, alpha-carotene, and lutein.

While the current dietary recommendation is for five servings of fruit and vegetables a day, Americans fall somewhat short of this goal. A recent survey showed that only 23 percent of the population is achieving this goal; the average daily intake is about three and a half servings of fruits and vegetables (Subar et al., 1992).

Vitamin C

Vitamin C is found in fruits, particularly citrus fruits and juices, and in green vegetables, as well as in some fortified foods. Of a group of epidemiologic studies investigating the role of vitamin C, three-fourths found that vitamin C, or fruit rich in vitamin C, provides significant protection (Block 1991). The evidence is most consistent for cancers of the esophagus, oral cavity, and stomach, but protective effects have been reported for cancers of the pancreas, rectum, and cervix. There is increasing evidence for a role in lung cancer, and an analysis combining results of studies of diet and breast cancer found that vitamin C had a strong and significant negative association (Howe et al., 1990).

Other Nutrients

Fruits, vegetables, and grains contain other vitamins and minerals associated with a protective effect against cancer.

Vitamin E has inhibited tumors in experimental animals and been linked to reduced risks of oral, stomach, and other cancer in epidemiologic studies. Selenium also may have a protective effect. In a recent randomized large-population trial testing the effectiveness of vitamin/mineral supplementation among persons in high risk areas of China, those who received daily supplements with a combination of beta-carotene, vitamin E, and selenium for 5 years had a significantly lower cancer death rate (Blot et al., 1993). The findings do not automatically translate to Western populations—in that the Chinese population studied was chronically deficient in a number of nutrients—but offer a hopeful sign that certain vitamins and minerals may lower risk of some cancers. However, two other recent large randomized trials of supplements, one testing the effect of supplemental beta-carotene or alpha-tocopherol in the prevention of lung cancer among smokers and the other testing the effect of supplemental beta-carotene and vitamins C and E in the prevention of adenomatous polyps (a precursor lesion for colorectal cancer), suggest that supplemental use of these nutrients does not reduce the risk of either lung or colorectal cancer (The ATBC Study Group, 1994; Greenberg et al., 1994). In the study of the effect of beta-carotene or alpha-tocopherol on lung cancer among smokers, dietary intake of these nutrients from foods was associated with a reduced risk for lung cancer (The ATBC Study Group, 1994). Some studies suggest that calcium may play a protective role in colon cancer. A 19-year prospective study in men showed the risk for colon cancer was lower in those with the highest calcium intake (Garland, 1985). In addition to dairy products, certain vegetables are good sources of calcium, notably roots, okra, and dark green leafy vegetables such as collard greens.

Diet and Cancer Risk

REFERENCES

- The ATBC Cancer Prevention Study Group: The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 330:1029-35, 1994.
- Block G, Patterson B and Subar A: Fruit, vegetables, and cancer prevention: A review of the epidemiologic evidence. *Nutr Cancer* 18:1-29, 1992.
- Block G: Vitamin C and cancer prevention: The epidemiologic evidence. *Am J Clin Nutr* 53:270S-282S, 1991.
- Blot WJ, Li JY, Taylor PR, et al.: Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 85:1183-1192, 1993.
- Boyd NE, Cousins M, Lockwood G, et al.: The feasibility of testing experimentally the dietary fat-breast cancer hypothesis. *Br J Cancer* 62:878-881, 1990.
- Committee on Diet, Nutrition, and Cancer: Assembly of Life Sciences, National Research Council. Diet, Nutrition, and Cancer. Washington, DC: National Academy Press, 1982.
- Doll R and Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66:1191-1308, 1981.
- Garland C, Barrett-Connor E, Rossof AH, et al.: Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* 1:307-309, 1985.
- Giovannucci E, Stampfer MJ, Colditz G, et al.: Relationship of diet to risk of colorectal adenoma in men. *J Natl Cancer Inst* 84:91-98, 1992.
- Greenberg ER, Baron JA, Tosteson TD, et al.: A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 331:141-147, 1994.
- Henderson MM, Kushi LH, Thompson DJ, et al.: Feasibility of a randomized trial of a low-fat diet for the prevention of breast cancer: dietary compliance in the Women's Health Trial Vanguard Study. *Prev Med* 19:115-133, 1990.
- Howe GR, Friedenreich MJ, Meera J, et al.: A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst* 83:336-340, 1991.
- Howe GR, Tomio HT, Gregory H, et al.: Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. *J Natl Cancer Inst* 82:561-569, 1990.
- Hursting SD, Thornquist M and Henderson MM: Types of dietary fat and the incidence of cancer at five sites. *Prev Med* 19:242-253, 1990.
- Kolonel LN: Fat and colon cancer: How firm is the evidence? *Am J Clin Nutr* 45:36-41, 1987.
- Lanza E, Shankar S and Trock B: Dietary fiber. In: *Macronutrients: Investigating their role in cancer*. (Micozzi MS, Moon TE, eds). New York: Marcel Dekker, Inc., 293-319, 1992.
- National Research Council, Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences. Diet and Health: Implications for Reducing Chronic Disease Risk. Washington, DC: National Academy Press, 1989.
- Subar AS, Heimendinger J and Krebs-Smith S: 5-A-Day for better health: a baseline study of American fruit and vegetable consumption. NCI, NIH, Rockville, MD (Executive summary), 1992.
- Steinmetz KA and Potter JD: Vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes Control* 2:325-357, 1991. (Review article).
- Trock B, Lanza E and Greenwald P: Dietary fiber, vegetables and colon cancer: Critical review and meta-analysis of the epidemiologic evidence. *J Natl Cancer Inst* 82:650-661, 1990.
- U.S. Department of Agriculture, U.S. Department of Health and Human Services. Nutrition and your health: Dietary guidelines for Americans. Washington, DC: Home and Garden Bulletin No. 232. Government Printing Office, 1980.
- U.S. Department of Health and Human Services: The Surgeon General's Report on Nutrition and Health. DHHS (PHS) Publ. No. 88-50210. Washington, DC: Dept. of Health and Human Services, Public Health Service, 1988.
- Willett WC, Stampfer MJ, Colditz GA, et al.: Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323:1664-1672, 1990.
- Willett WC, Hunter DJ, Stampfer MJ, et al.: Dietary fat and fiber in relation to risk of breast cancer. *JAMA* 268:2037-2081, 1992.
- Ziegler RG: A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J Nutr* 119:116-122, 1989.

Most cancers are caused by a variable mix of heredity and environment (Knudson, 1985). While an inherited defect can lead to cancer clusters in multiple members of certain families, the age at which cancers first appear will differ among these relatives, due in part to environmental triggers (Li et al, 1989). Other cancers, such as lung cancers in cigarette smokers, while caused primarily by external factors, are still influenced by genes which modify an individual's risk of disease. To further our understanding of cancer etiology and risk factors, scientists are currently studying the complex ways in which genes and environment interact.

Some ethnic groups apparently possess traits that protect them against specific cancers. For example, chronic lymphocytic leukemia is extremely rare among Asians; Ewing's sarcoma, skin cancers, and testicular cancer are very rare among blacks.

Family clusters have been reported for virtually every form of cancer (Li, 1988). In general, close relatives of a cancer patient have twice the usual risk for developing the same type of cancer, but among different cancer families the level of excess risk can vary widely. Familial cancer clusters are often due to inherited factors, but environmental influences, chance association, or a combination of these factors also must be considered. The effect of chance is considerable; within the U.S. population there is approximately a 45 percent lifetime risk of developing cancer, including the common nonmelanoma skin cancers (Li, 1990). Thus, it is not unusual for most families to have at least some individuals with a history of cancer (Mulvihill, 1985).

An inherited susceptibility often becomes apparent when cancers of the same body site or organ occur in multiple blood relatives (Lynch and Lynch, 1993). These cancers tend to occur at earlier ages than usual, and often develop in more than one site in a particular organ, e.g., two primary breast cancers in the same breast or one in each breast. Hereditary cancers can also arise in multiple organs, as seen in the Li-Fraumeni syndrome, a disorder characterized by the early onset of breast cancer in mothers of children with leukemia and/or bone and soft tissue sarcomas (Srivastava et al, 1990). In addition, cancer can occur as part of a non-cancerous hereditary disease with diverse features, such as neurofibromatosis.

In familial cancers that are triggered by environmental carcinogens, patient education regarding the avoidance of harmful exposures can help prevent or delay the onset of cancer. For example, members of melanoma-prone families who avoid significant ultraviolet radiation exposure can reduce substantially their risk of melanoma.

Familial Factors

Frederick P. Li, M.D.,^a
Mary C. Fraser, R.N., M.A.^b

^a From the Dana Farber Institute,
Boston, Massachusetts

^b From the Department of Nursing,
Warren G. Magnuson Clinical Center,
and the Genetic Epidemiology
Branch, National Cancer Institute,
Bethesda, Maryland

Familial Factors

Recent laboratory findings have emphasized the importance of studying cancer-prone families (Benz, 1990). New methods in molecular biology have been used to identify several human cancer genes and to reveal a new class of cancer genes, called tumor suppressor genes or antioncogenes (Friend et al, 1988). These genes normally function by inhibiting the development of cancer. However, when they are damaged they lose their protective effect and cancer arises with greater frequency. The first such inherited cancer susceptibility gene to be discovered was that for retinoblastoma (RB1), a malignant eye tumor which occurs in children (Friend, 1988).

Several additional tumor suppressor genes have been identified, predominantly through studies of cancer-prone families with hereditary cancers (Li, 1993). For example, inherited alterations in the p53 gene have been found in the Li-Fraumeni Syndrome (Srivastava et al, 1990). The WT1 gene for Wilms' tumor, the APC gene for colon cancers associated with familial adenomatous polyposis coli, the NF1 and NF2 genes for neurofibromatosis, types 1 and 2, the p16 gene found in some melanoma families, and the VHL gene for renal cancer and other tumors associated with von Hippel-Lindau disease have all been recently identified and characterized (Li, in press).

Major discoveries within the last year include the identification of BRCA1, a gene for hereditary breast and ovarian cancer, the localization of BRCA2, another breast cancer gene, and mismatch repair genes—such as MLH1 and MSH2 for hereditary nonpolyposis colorectal cancer (Bronner, et al, 1994, Futreal, et al, 1994, Miki et al, 1994). (The function of mismatch repair genes is to prevent DNA from making errors during replication.) Approximately 5 percent of breast or colon cancer patients might carry one or more inherited susceptibility genes. The discovery of these genes has increased greatly the numbers of cancer susceptibility gene carriers who can possibly be identified (Peters, 1994, Ollit and Brown, 1994).

The primary purpose of identifying gene carriers would be to promote earlier detection of cancer and, since prognosis is correlated closely with stage of disease at diagnosis, increased survivability (Parry et al, 1987, Wattenberg, 1993). However, identifying gene carriers in cancer-free populations is a new concept with many clinical, ethical, legal and psychosocial implications yet to be explored (Lerman et al, 1991, American Society of Human Genetics, 1994, Li et al, 1992). Predisposition testing presents certain advantages when prevention and early detection measures are available. On the other hand, there is a great potential for harm—from loss of insurability and employability, psychological stress, social stigmatization and other adverse consequences. As more and more inherited susceptibility genes are identified, their clinical relevance will require careful evaluation. The challenge to research is to identify testing procedures and guidelines that maximize benefits while minimizing harm (Loescher, 1995).

REFERENCES

- Benz EJ: The molecular genetics of cancer: Introduction to principles of recombinant DNA technology. *Cancer* 65:731-741, 1990.
- Bronner CE, Baker SM, Morrison PT et al: Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary nonpolyposis colon cancer. *Nature* 368:258-261, 1994.
- Friend SH, Dryja TP, Weinberg RA: Oncogenes and tumor-suppressing genes. *N Engl J Med* 318:618-622, 1988.
- Futreal PA, Liu Q, Shattuck-Eidens D, et al: BRCA1 mutations in primary breast and ovarian carcinomas. *Science* 266:120-122, 1994.
- Knudson AG Jr: Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res* 45:1437-1443, 1985.
- Lerman C, Rimer BK and Engstrom PF: Cancer risk notification: psychosocial and ethical implications. *J Clin Oncol* 9:1275, 1991.
- Li, FP: Identification and management of inherited cancer susceptibility. Environmental Health Perspectives, in press.
- Li FP: Molecular epidemiology studies of cancer in families. *Brit J Cancer* 68:217-219, 1993.
- Li FP: Familial cancer syndromes and clusters. *Curr Prob Cancer* 14:73-114, 1990.
- Li FP, Garber JE, Friend SH, et al: Recommendations on predictive testing for germ line p53 mutations among cancer-prone individuals. *J Natl Cancer Inst* 84:1156-1160, 1992.
- Li FP: Cancer families: Human models of susceptibility to neoplasia - The Richard and Hinda Rosenthal Foundation Award lecture. *Cancer Res.* 48:5381-5386, 1988.
- Li FP, Dreyfus MG and Antman KH: Asbestos-contaminated nappies and familial mesothelioma. *Lancet* 1:909-910, 1989.
- Loescher LJ: Genetics in cancer prediction, screening, and counseling: Part 1, genetics in cancer prediction and screening. *Oncol Nurs Forum* 22:10-15, 1995.
- Lynch HT and Lynch JF: Familial factors and genetic predisposition to cancer: Population studies. *Cancer Detection and Prevention* 15(1):49-57, 1991.
- Miki Y, Swensen J, Shattuck-Eldens D et al: Isolation of BRCA1, the 17q-linked breast and ovarian cancer susceptibility gene. *Science* 266:61-71, 1994.
- Mulvihill JJ: Clinical ecogenetics — cancer in families. *New Engl J Med* 312:1569-1570, 1985.
- Offit K, Brown K: Quantitating familial cancer risk: a resource for clinical oncologists. *J Clin Oncol* 12:1724-1736, 1994.
- Parry DM, Mulvihill JJ and Miller RW: Strategies for controlling cancer through genetics. *Cancer Res* 47:6814-6817, 1987.
- Peters JA: Familial cancer risk - Part I: impact on today's oncology practice. *The Journal of Oncology Management* Sept./Oct.:18-30, 1994.
- Srivastava S, Zou ZQ, Pirolo K et al: Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature* 348:747-749, 1990.
- Statement of the American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition. *Am J Hum Genet* 55(5):i-iv, 1994.
- Wattenberg LW: Prevention-therapy-basic science and the resolution of the cancer problem. *Cancer Res* 53:5890-5896, 1993.

Herpes Simplex Virus Type 2 and Human Papillomaviruses

Allan Hildesheim, Ph.D.*

Since the carcinogenic potential of viruses was first recognized by Rous in 1911, numerous additional viruses have been shown or hypothesized to be linked to the development of various cancers in humans (Evans et al., 1990; Rawls et al., 1977; Reeves et al., 1989b).

Herpes simplex virus type 2 (HSV-2) is one such virus. HSV-2 belongs to the herpes family of viruses, which also includes HSV-1, a virus known to infect the oral mucosa and to result in canker sores. HSV-2 is a sexually transmitted virus that has a predilection for infecting male and female genitalia, although it has also been shown to infect the oral mucosa (Corey et al., 1986b). An important feature of HSV-2 is its ability to become latent and to persist in the host for many years after infection (Corey et al., 1986a). HSV-2 infection can be either symptomatic or asymptomatic. The frequency of infections that result in symptoms is unknown. However, serologic studies that have measured the prevalence of HSV-2 antibodies in different populations indicate that a sizable proportion of infections with this virus are likely to be asymptomatic. Given the fact that these asymptomatic infections do not come to the attention of the medical community, it has been difficult to determine the overall prevalence of this virus. Nonetheless, one study that examined HSV-2 antibody levels among participants of the National Health and Nutrition Examination Survey reported an overall prevalence of 16.4 percent (Johnson et al., 1989). This indicates that nearly one in five individuals in the population may be carriers of the HSV-2 virus, with the figure being even higher in certain segments of the population.

In the late 1960s and 1970s, several studies indicated that women exposed to HSV-2 were at two- to four-fold elevated risks of developing cervical cancer (Kaufman et al., 1986). Laboratory evidence supported this hypothesis; in-vitro and in-vivo studies demonstrated the transforming ability of HSV-2 as well as its potential carcinogenic effects (Wentz et al., 1983). However, more recent evidence suggests that, while HSV-2 might be involved in the development of cervical cancer, it is not likely to play as important a role as was once believed. Evidence now points to human papilloma viruses (HPV) as the viruses that are likely to play a central role in the development of this disease (Reeves et al., 1989b; Koutsky et al., 1988).

HPV comprises a family of viruses that includes upwards of 60 viral types. These viruses are known to be the cause of warts at various sites. About 20 types have been shown to infect the genital area (Koutsky et al., 1988). In addition, various HPV types are known to infect the skin, oral cavity, larynx, and anus. As is the case of HSV-2, a large proportion of HPV infections are asymptomatic and may therefore go undetected. This has made it difficult to determine the prevalence of this

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

virus in the general population; most estimates range from 10 to 40 percent, depending on the population studied, the method used to detect the virus, and the viral types detected (Koutsky et al., 1988).

The association between HPV and cervical cancer was first suggested by Harold zur Hausen in 1974 (zur Hausen, 1974). Since that time, numerous epidemiologic and laboratory studies have supported an association between HPV and cervical cancer (Reeves et al., 1989b; Koutsky et al., 1988). It has been demonstrated that women who are infected with HPV are at higher risk of developing cervical intraepithelial neoplasia (a benign precursor of cervical cancer) as well as cervical cancer. It is estimated, from case-control studies, that women infected with HPV are 10 or more times more likely to develop cervical cancer than women who are HPV-negative (Koutsky et al., 1988; Reeves et al., 1989a). In vitro laboratory studies have been able to isolate those fragments of the HPV DNA that are likely to be responsible for its ability to transform cells in humans, and HPV DNA fragments have been detected in tumor samples obtained from cervical cancer patients.

Given the high prevalence of HPV infection relative to the incidence of cervical cancer, it is believed that HPV alone is not capable of inducing cervical cancer and that exposure to other factors, called cofactors, must be important determinants of which HPV infected women will develop the disease. Numerous exposures are currently under investigation as possible cofactors. These include host factors such as immunological status, including infection with HIV, as well as environmental exposures such as smoking, oral contraceptive use, diet, parity, and other sexually transmitted diseases, including HSV-2.

HSV-2 and HPV are also believed to be associated with the development of other cancers. However, less is known about the link between these viruses and cancers of other sites. Limited evidence suggests that HSV-2 might be involved in the etiology of other genital cancers (Kaufman et al., 1981). HPV has been linked to numerous cancers, including other genital tumors, as well as skin, oral, laryngeal, and anal cancers, but causation is less firmly established.

Herpes Simplex Virus Type 2 and Human Papillomaviruses

REFERENCES

- Corey L, and Spear PG: Infections with herpes simplex viruses (1). *N Eng J Med* 314(11):686-691, 1986a.
- Corey L, and Spear PG: Infections with herpes simplex viruses (2). *N Eng J Med* 314(12):749-757, 1986b.
- Evans AS and Mueller NE: Viruses and cancer: Causal associations. *Ann Epidemiol* 1(1):71-92, 1990.
- Johnson RE, Nahmias AJ, Magder LS, et al.: A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Eng J Med* 321:7-12, 1989.
- Kaulman RH and Adam E: Herpes simplex virus and human papilloma virus in the development of cervical cancer. *Clin Obstet Gynecol* 29(3):678-692, 1986.
- Kaulman RH, Dreesman GR, Burek J, et al.: Herpesvirus-induced antigens in squamous-cell carcinoma in situ of the vulva. *N Eng J Med* 305:183-188, 1981.
- Koutsky LA, Galloway DA and Holmes KK: Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 10:122-163, 1988.
- Rawls WE, Bacchetti S and Graham FL: Relation of herpes simplex virus to human malignancies. *Curr Top Microbiol Immunol* 77:71-75, 1977.
- Reeves WC, Brinton LA, Garcia M, et al.: Human papillomavirus infection and cervical cancer in Latin America. *N Eng J Med* 320:1437-1441, 1989a.
- Reeves WC, Rawls WE and Brinton LA: Epidemiology of genital papillomaviruses and cervical cancer. *Rev Infect Dis* 11(3):426-439, 1989b.
- Wentz WB, Heggie AD, Anthony DD, et al.: Effect of prior immunization on induction of cervical cancer in mice by herpes simplex virus type 2. *Science* 222:1128-1129, 1983.
- zur Hausen H, Meinhol W, Scheiber W et al.: Attempts to detect virus-specific DNA in human tumors. I. Nucleic acid hybridization with complementary RNA of human wart virus. *Int J Cancer* 13:650-656, 1974.

Hormones

Catherine Schairer, Ph.D.*

Hormones, substances produced in the body, have regulatory effects on specific organs. Estrogens and progesterone are two hormones produced predominantly in the ovary of the female. Estrogens control the development of feminine body characteristics, and both estrogens and progesterone regulate the menstrual cycle and pregnancy. Androgens, which are produced predominantly in the male, determine masculine body characteristics. These hormones, or synthetic chemicals that have similar effects, are used as drugs for a variety of purposes.

Many women take "replacement" estrogens to relieve the hot flashes, vaginal dryness, and itching that may develop at menopause when ovarian function decreases. They are also taken by older women to retard bone loss. The most frequently prescribed estrogen in the United States is Premarin, a natural estrogen. Between 1962 and 1975, there was a four-fold increase in the use of estrogens for menopausal symptoms in the United States. This was followed by a parallel increase in the incidence of cancer of the endometrium, the lining of the uterus (Thomas, 1988). An explanation for the rise in incidence came from several studies which showed nine- to 14-fold increases in the risk of endometrial cancer associated with long-term use of menopausal estrogens. Subsequent studies have confirmed these earlier findings and suggest that risk is greatest among current and recent users. There is also a fairly rapid decline in risk after cessation of use, although a small increase in risk remains for former users (Brinton, 1984).

Numerous studies have shown a slightly increased risk of breast cancer in different subgroups of women who have used estrogens for a long period or at relatively high doses. A number of other studies, however, have found no increased risk associated with duration or dose, making it difficult to draw firm conclusions about the risk of breast cancer associated with the use of estrogen replacement therapy (Brinton et al., 1993).

Most evidence suggests no overall association between menopausal estrogen use and risk of ovarian cancer (Brinton, 1984), although further research is needed to determine whether replacement estrogens increase risk of specific types of ovarian tumors (Thomas, 1988). Of two studies that have examined the relationship between menopausal estrogens and eye melanoma, one found no association (Gallagher et al., 1985), and the other found a two-fold increase in risk associated with menopausal estrogen use (Hartge et al., 1989). Several studies suggest that menopausal estrogens protect against large bowel cancer (Burch et al., 1975; Furner et al., 1989), while others do not (Weiss et al., 1981; Potter et al., 1983; Davis et al., 1989).

With the recognition in the early 1980s that use of progesterone or its derivatives (collectively called progestins) may offset the increased risk of endometrial cancer associated with estrogen use, it has become increasingly common to prescribe progestins in conjunction with estrogens during a portion of the monthly cycle.

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Hormones

The most frequently prescribed progestin in the United States is Provera (medroxy-progesterone acetate), a derivative of progesterone. While the addition of progestins to estrogen replacement therapy appears to have definite beneficial effects on endometrial cancer risk (Persson et al., 1989; Voigt et al., 1991; Brinton et al., 1993; Jick, et al., 1993), further epidemiologic studies are needed to determine the optimal regimen needed to counteract the adverse effects of estrogens, particularly after prolonged use. Data regarding the effect of estrogen/progestin replacement therapy on risk of breast cancer are limited and inconsistent. Early studies reported a protective effect of the estrogen/progestin combination, but a recent study reported an increased risk of breast cancer in long-term users of estrogens and progestin in combination (Kelsey and Gammon, 1990). Further studies are needed to clarify this issue.

In contrast to the natural estrogens most commonly used in estrogen replacement therapy, the estrogens used in oral contraceptives are synthetic. The most effective and widely used oral contraceptives are "combination" pills, taken for 21 days, that contain a fixed amount of estrogen and progestin. These "combination" oral contraceptives actually reduce a woman's risk of some cancers. Studies have uniformly shown a risk reduction of 40 to 50 percent for ovarian and endometrial cancers in women who ever used combined pills. The risk decreases with increasing duration of use, and some protective effect appears to persist for at least 10 to 20 years after discontinuation of use (Stanford, 1993; Rosenberg, 1994). However, sequential oral contraceptives, in which estrogen alone is taken during the first 14 to 16 days of the monthly cycle followed by an estrogen-progestin combination during the last five or six days, have been associated with increases in the risk of endometrial cancer (Van Leeuwen and Rookus, 1989).

The relationship between oral contraceptive use and risk of breast cancer remains unresolved despite numerous studies. Although many studies have found that oral contraceptive use does not increase risk of breast cancer in most women, most, but not all, studies have reported that long-term use at an early age increases risk in women under the age of 45 years (Kelsey and Gammon, 1990). Prolonged use of oral contraceptives has also been linked to an increased risk of cervical cancer (Brinton, 1991), but some doubt remains as to the causality of this association. Substantial increases in the risk of liver cancer have also been associated with oral contraceptive use in developed countries where this cancer is very rare (Rosenberg, 1991). However, no such elevation in risk has been detected in countries where hepatitis B virus is endemic and liver cancer rates are high (WHO, 1989). Present evidence suggests that there is no causal link between oral contraceptive use and cutaneous melanoma, cancers of the kidney, the colon, the gallbladder, or tumors of the pituitary (Milne and Vessey, 1991).

Depot-medroxyprogesterone acetate (DMPA), a long-acting progestational injectable contraceptive, has been approved for contraceptive use in more than

Hormones

90 countries, including the United States. However, concern that DMPA might increase the risk of breast cancer in women delayed its approval in the United States until 1992. Although data are limited, there appears to be no overall increase in breast cancer risk among women who have used this form of contraception. However, a two-fold increase in the risk of breast cancer in women who started using DMPA in the previous five years has been reported, suggesting that DMPA may accelerate the growth of preexisting tumors (Skegg, 1995). Data on DMPA use and risk of other cancers are also limited, but suggest no association with cervical or ovarian cancer (WHO, 1993), or liver cancer (WHO 1991), and a protective effect against endometrial cancer (WHO, 1993).

DES (diethylstilbestrol), a synthetic chemical with estrogenic properties, has also been linked to risk of cancer. It was used for the prevention of miscarriage and late complications of pregnancy during the late 1940s and 1950s. Following several studies in the late 1950s that reported no beneficial effect of DES, use of the drug gradually tapered off (Vessey, 1989). In 1971, prenatal DES exposure was linked in young women to clear-cell adenocarcinoma of the vagina, a rare form of cancer. Subsequent studies have also linked prenatal DES exposure to clear-cell adenocarcinoma of the cervix. Results from a number of studies suggest that a woman exposed to DES in utero has about a one in 1,000 chance of developing a clear-cell adenocarcinoma of the vagina or cervix by the age of 34 years (Vessey, 1989). There is little evidence, however, that prenatal exposure to DES increases risk of other types of cervical or vaginal cancers (Thomas, 1988).

Studies have shown that males exposed to DES in utero have a greater frequency of abnormalities of the reproductive tract than those not exposed. One of these abnormalities, failure of the testes to descend into the scrotum, is known to increase the risk of testicular cancer. In several studies, a higher proportion of males with testicular cancer were also exposed to DES in utero compared to study subjects without testicular cancer (IARC, 1987).

Studies of breast cancer in women who were themselves treated with DES to prevent abortion have yielded inconsistent results and further studies are needed to determine whether the possible association is causal (Thomas, 1988). Data on development of other types of cancer in women exposed to DES during pregnancy are too limited to draw firm conclusions (IARC, 1987).

Synthetic androgens are used in the treatment of renal conditions, various types of anemias, endocrine disorders, and generalized weakness. They are also used by athletes and body builders to enhance development of skeletal muscles. Individual cases of liver cancer have been linked to the use of these substances, but well-designed studies are needed to confirm or refute a causal relationship with oral contraceptives (IARC, 1987).

REFERENCES

- Brinton LA: The relationship of exogenous estrogens to cancer risk. *Cancer Detect Prevent* 7:159-171, 1984.
- Brinton LA: Estrogen replacement therapy and endometrial cancer: Unresolved issues. *Obstet Gynecol* 81:265-271, 1993.
- Brinton LA and Schairer C: Estrogen replacement therapy and breast cancer risk. *Epidemiologic Reviews* 15:66-79, 1993.
- Burch JC, Byrd BF and Vaughn WK: The effects of long-term estrogen administration to women following hysterectomy. *Front Horm Res* 3:208-214, 1975.
- Davis FG, Furner SE, Persky V, et al.: The influence of parity and exogenous female hormones on the risk of colorectal cancer. *Int J Cancer* 43:587-590, 1989.
- Furner SE, Davis FG, Nelson RL, et al.: A case-control study of large bowel cancer and hormone exposure in women. *Cancer Res* 49:4936-4940, 1989.
- Gallagher RP, Elwood JM, Rootman J, et al.: Risk factors for ocular melanoma: Western Canada melanoma study. *J Natl Cancer Inst* 71:775-778, 1985.
- Hartge P, Tucker MA, Shields JA, et al.: Case-control study of female hormones and eye melanoma. *Cancer Res* 49:4622-4625, 1989.
- International Agency for Research on Cancer: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs vols 1 to 42. [Suppl 7], 1987.
- Kelsey JL and Gammon MD: Epidemiology of breast cancer. *Epidemiol Rev* 12:228-240, 1990.
- Milne R and Vessey M: The association of oral contraception with kidney cancer, colon cancer, gallbladder cancer (including extrahepatic bile duct cancer) and pituitary tumors. *Contraception* 43:667-693, 1991.
- Persson I, Adami HO, Bergkvist L, et al.: The risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *BMJ* 298(6667):147-151, 1989.
- Potter JD and McMichael AJ: Large bowel cancer in women in relation to reproductive and hormonal factors: A case-control study. *J Natl Cancer Inst* 71:703-709, 1983.
- Rosenberg L: The risk of liver neoplasia in relation to combined oral contraceptive use. *Contraception* 43:643-652, 1991.
- Skegg DCG, Noonan EA, Paul C, et al.: Depot-medroxyprogesterone acetate and breast cancer: a pooled analysis of the World Health Organization and New Zealand studies. *JAMA* 273:799-804, 1994.
- Stanford JL, Brinton LA, Berman ML, et al.: Oral contraceptives and endometrial cancer risk: Do other risk factors modify the association? *Int J Cancer* 54:243-248, 1993.
- Thomas DB: Steroid hormones and medications that alter cancer risks. *Cancer* 62:1755-1767, 1988.
- Van Leeuwen FE and Rookus MA: The role of exogenous hormones in the epidemiology of breast, ovarian and endometrial cancer. *Eur J Cancer Clin Oncol* 25:1961-1972, 1989.
- Vessey MP: Epidemiologic studies of the effects of diethylstilboestrol. In Perinatal and Multigeneration Carcinogenesis, IARC Scientific Publication No. 96, pp 335-348, 1989.
- Vessey M and Grice D: Carcinoma of the cervix and oral contraceptives: epidemiological studies. *Biomed Pharmacother* 43:157-160, 1989.
- Weiss NS and Daling JR and Chow WH: Incidence of cancer of the large bowel in relation to reproductive and hormonal factors. *J Natl Cancer Inst* 67:57-60, 1981.
- World Health Organization: Depot-medroxyprogesterone acetate (DMPA) and cancer: Memorandum from a WHO meeting. *Bull World Health Organ* 64:375-382, 1986.
- World Health Organization: Combined oral contraceptives and liver cancer. *Int J Cancer* 43:254-259, 1989.
- World Health Organization: Depot-medroxyprogesterone acetate (DMPA) and risk of liver cancer. *Int J Cancer* 49:182-185, 1991.

Drugs that suppress the immune system are given to organ transplant patients to prevent the body from rejecting the donor organ. More recently, these drugs have also been used to treat a variety of autoimmune diseases, including severe rheumatoid arthritis. Azathioprine, adrenal corticosteroid hormones, and cyclosporin A are the most widely used immunosuppressive drugs, although other drugs, particularly many of the anticancer drugs, have immunosuppressive side effects in addition to the effects for which they are used.

Among transplant recipients treated aggressively with immunosuppressants, the risk of non-Hodgkin's lymphoma is increased to 50-fold or greater (Kinlen, 1992).

These lymphomas often arise rapidly—within a year or two—after the transplant operation. They often develop in the brain, an unusual site for this type of cancer (Hoover, 1977). Some other cancers—skin cancers, soft-tissue (including Kaposi's sarcoma), as well as malignant melanoma, also occur at a higher rate in transplant recipients, although not nearly at the magnitude seen for the lymphomas.

Patients treated with these drugs for autoimmune diseases—generally at much lower doses—have about a ten-fold increased risk of lymphoma, adding to the evidence, from a number of sources, that the risk of this tumor is directly related to the intensity of the immunosuppressive treatment.

Other Drugs

Radioactive drugs contain a molecule “tagged” with a radioactive isotope; that isotope can be counted or imaged in diagnostic tests. Radioactive drugs can concentrate in body tissues and, depending on their strength and half-life, may injure those tissues. Radioactive drugs have also been used to treat tuberculosis of the bone, thyroid cancer, and the blood disorder polycythemia vera. Some of these radioactive drugs have been shown to cause various cancers, including osteogenic sarcoma, a type of bone cancer; leukemia; and a rare form of liver cancer (Hoover and Fraumeni, 1981).

In 1964, chlornaphazine, a drug used to treat polycythemia vera and Hodgkin's lymphoma, was withdrawn from the market because it was found to cause bladder cancer. Chlornaphazine is chemically related to beta-naphthylamine, a chemical earlier associated with bladder cancer among workers in the dye industry. Drugs containing inorganic arsenicals (e.g., Fowler's solution) are also no longer in clinical use. However, studies have shown that they can cause skin cancer. These cancers are typically multiple, involve unexposed parts of the body and unusual locations, and are associated with arsenical pigmentation and hyperkeratosis.

Immunosuppressives and Other Drugs

Robert N. Hoover, M.D.*

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Immunosuppressives and Other Drugs

Other drugs have also been found to increase the rate of human cancers. Pain-killing drugs that contain phenacetin have been linked to kidney cancers, and a photochemotherapy regimen for psoriasis which combines methoxysporalens with ultraviolet-A exposure (PUVA) has been linked with skin cancer.

For a number of other medications there is some evidence of a cancer hazard, but conflicting studies or other inconsistencies in the evidence make them merely suspect. For two such categories of drugs, coal tar ointments and thiazide diuretics, the accumulating evidence is particularly worrisome. Coal tar ointments contain known carcinogenic chemicals (polycyclic hydrocarbons), and the relationship of use of these ointments to risk of skin cancer has been a matter of debate for some time. The evidence from studies of psoriasis patients treated with high doses over protracted periods at this time seems to indicate an excess risk. The data concerning a possible relationship between use of thiazide diuretics and excess risk of kidney cancer illustrate one of the problems in interpreting any drug-cancer association, that is, the ability to separate a drug effect from an effect of the condition for which the drug is prescribed. There have now been more than ten studies, of various designs, which have identified an excess risk of kidney cancer among users of thiazide diuretics. To date, it has not been possible to disentangle the effect of the drug from a potential effect of high blood pressure—the reason the drug was prescribed in the vast majority of patients in these studies. With the high prevalence of use of this medication, clarifying these relationships should have a high priority.

There are occasional suggestions that some medications may actually be associated with a reduced risk of cancer. Perhaps most provocative of these has been the recent observation that frequent users of aspirin or other nonsteroidal anti-inflammatory drugs experience fewer cancers of the colon than expected (Thun, 1991).

It may even be that some medications will be found to be protective against some cancers while causing others. This seems to be the emerging pattern associated with the use of tamoxifen. Women taking this drug as part of a treatment regimen for breast cancer experience a substantially reduced incidence of a second primary breast cancer compared to breast cancer patients who don't receive the drug. Conversely, the drug appears to be associated with an increased risk of cancers of the lining of the uterus (endometrium). This would be consistent with the differing hormonal effects this drug has in these two organs, since it acts as an estrogen in the uterus and as an antiestrogen in the breast (Nayfield et al., 1991; Fisher et al., 1994).

REFERENCES

- Fisher B, Costantino JP, Redmond CK, et al.: Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) b-14. *J Natl Cancer Inst* 86:527-537, 1994.
- Hiatt RA, Tolan K and Quesenberry CP Jr: Renal cell carcinoma and thiazide use: a historical, case-control study. *Cancer Causes Control* 5:319-325, 1994.
- Hoover R and Fraumeni JF Jr: Drug-induced cancer. *Cancer*, 47:1071-1080, 1981.
- Hoover R: Effects of drugs: immunosuppression. (Hiatt, Watson, Winsten, eds.). In *Origins of Human Cancer*. Cold Spring Harbor Lab. Press 369-379, 1977.
- Hoover RN: Cancer induced by cancer treatment. (Fortner, Rhoads, eds.). In *Accomplishments in Cancer Research*, 1992. Philadelphia: J.B. Lippincott, 1994, 229-239.
- Kinlen LJ: Immunosuppressive therapy and acquired immunological disorders. *Cancer Res [suppl]* 52:5474s-5476s, 1992.
- Nayfield S, Karp JE, Ford LG, et al.: Potential role of tamoxifen in prevention of breast cancer. *J Natl Cancer Inst* 83:1450-1459, 1991.
- Thun MJ, Namboodiri MM, Heath CW Jr: Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 325(23):1593-1596, 1991.

Ionizing Radiation

John D. Boice, Sc.D.*

Ionizing radiation is a known cause of cancer and other adverse effects. It is one of the most extensively studied human carcinogens and may account for about 3 percent of all cancers (NAS, 1990). Ionizing radiation is able to remove electrons from atoms and to change the molecular structures of cells. It is these cellular changes that may cause cancer to develop. The genetic DNA in the cell nucleus is thought to be the critical target for radiation-induced damage.

Some radiation comes from natural sources, such as that from cosmic rays and radioactive substances in the earth's crust. Each of us is exposed to this "background" radiation at a rate of about 1 to 2 mGy per year. (The gray [Gy] is a unit of measurement for the amount of radiation energy absorbed by body tissues. It is equal to 100 rad and is now the unit of dose.)

Very high doses of radiation (tens of gray) received all at once may be fatal, but if spread out over a period of time, a high dose of radiation may be less damaging to healthy tissues. A single, 5-Gy dose of whole-body irradiation, for example, would cause about half the people exposed to it to die within 30 days. But patients who receive daily radiation therapy treatments of 2 Gy directed to a small area of the body can be exposed to tens of gray over a period of weeks. It is difficult to measure the effects of low-level radiation (less than .25 Gy) from common sources like medical X-rays.

Some of what we now know about the effects of radiation exposure was learned by studying patients treated with radiation in the past. Some of the first quantitative evidence that radiation causes cancer came from studies of patients who received radiation therapy for ankylosing spondylitis, a spinal disorder, before 1954 (Darby et al., 1987). These patients were found to have more leukemia and cancers of the lung, esophagus, bone, and other organs within the irradiated field than would be expected in a healthy population. Second cancers following radiation treatments are rare but do occur. The most extensive survey, conducted among patients with cervical cancer, concluded that, at most, 5 percent of second cancers could be attributed to radiation therapy (Boice et al., 1988).

Between 1935 and 1954, fluoroscopy, an X-ray procedure, was used to monitor treatment of patients with tuberculosis; the women who were thus treated could receive an average dose of 1 Gy to the breast. Ten to 15 years later, these women had a high incidence of breast cancer (Boice et al., 1991).

There is a high risk of thyroid cancer many years after childhood exposure to radiation for therapy of noncancerous conditions of the head and neck. Exposure during childhood can be particularly damaging because rapidly growing cells may be more sensitive than slower-growing cells irradiated later in life. Before 1950, individuals with enlarged thymus glands were treated with intense radiation. An ele-

* From the Radiation Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Ionizing Radiation

vated risk of thyroid cancer and leukemia has since been found in this population (Shore et al., 1985). Similar increases have been observed following childhood irradiation for ringworm of the scalp (Ron et al., 1989). Those who may have received radiation treatments for thymus conditions or other childhood problems, such as scalp ringworm or enlarged tonsils, should alert their physicians.

Because the dangers of radiation were not recognized before the 1920s, radiologists who used X-rays extensively—and without shielding—in the early years of the century developed leukemia at excessive rates.

A classic study of women who painted radium dials before 1930 showed high rates of bone sarcomas and head cancers. They had swallowed large quantities of radioactive radium by licking their paint brushes to make fine tips; it has been estimated that the average dose reaching their bone tissues was very high—on the order of 17 Gy.

Much of our information about the effects of radiation comes from studies of atomic bomb survivors in Japan, among whom have been found increased rates of leukemia and cancers of the breast, thyroid, lung, stomach, and other organs (NAS, 1990). Female survivors who received a single dose of radiation from the blast were found to be at the same risk for breast cancer as women with tuberculosis who had repeated fluoroscopy exposures over a 3- to 5-year period. This suggests that in the case of breast cancer—but not necessarily other cancers—repeated small doses over the years may be as hazardous as a single, large dose. The risk, however, seemed to be inversely correlated to the age at exposure to the blast, with no apparent increased risk in women over the age of 40.

Today, many women at risk of developing breast cancer are periodically examined with low-dose breast X-rays known as mammography. For high-risk women, particularly over age 50, the benefits of detecting cancer early far outweigh the small risk of developing cancer from repeated mammograms.

While exposure to low levels of radiation before birth is associated with the development of cancer during childhood, especially leukemia (Bithell and Stewart, 1975), not all researchers are convinced that prenatal irradiation is the cause of childhood cancer. Individuals exposed prenatally during the atomic bomb blasts in Japan do not have higher cancer rates. The current practice is to use ultrasound, rather than X-rays, during pregnancy whenever possible.

Ionizing Radiation

There are other environmental and occupational exposures to radiation. Radioactive fallout, for example, is produced during nuclear weapons tests when airborne radioactive particles settle to the ground. One study showed that persons accidentally exposed to very high levels of fallout had an increased risk of thyroid cancer (NAS, 1990).

Uranium miners inhale radioactive radon gas produced underground by the natural decay of uranium and have high rates of respiratory cancer (Lubin et al., 1994). It is possible that an interaction between inhaled radioactive gas and smoking enhances the risk from the radon exposure. Radon is becoming a public health concern in some locations because of its presence in groundwater and building materials. Based on extrapolations from studies among underground miners, it has been estimated that as many as 10 percent of all lung cancer deaths may be related to indoor radon exposures (Lubin and Boice, 1989).

In general, the breast, thyroid, and bone marrow are most sensitive to the effects of ionizing radiation. There may be a minimum lag time after exposure of about two years before leukemia develops, and 10 to 15 years before other cancers develop.

Avoidance of unnecessary medical X-rays is one of the best ways to reduce exposure to ionizing radiation. However, in many instances, the benefits outweigh the risks, as in mammography for some women, as a tool for diagnosis of various diseases or injuries, and as an effective way to treat some cancers.

REFERENCES

- Bithell JF, Stewart AM: Pre-natal irradiation and childhood malignancy: a review of the British data from the Oxford Survey. *Br J Cancer* 31:271-287, 1975.
- Boice JD Jr, Engholm G, Kleinerman RA, et al.: Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res* 116:3-55, 1988.
- Boice JD Jr, Preston D, Davis FG, et al.: Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat Res*, 125:214-222, 1991.
- Darby SC, Doll R, Gill SK, et al.: Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. *Br J Cancer* 55:179-190, 1987.
- Lubin JH and Boice JD Jr: Estimating Radon-induced lung cancer in the United States. *Health Phys* 57:417-427, 1989.
- Lubin JH, Boice JD Jr, Edling C, et al.: Radon and lung cancer risk: a joint analysis of 11 underground miners studies. National Cancer Institute. NIH Publ. No. 94-3644, Bethesda, Md, 1994.
- NAS: Health Risks of Radon and Other Internally Deposited Alpha-Emitters (BEIR IV Report). Washington, DC: Nat Acad Press, 1988.
- NAS: Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR 4). Washington, DC: Natl Acad Press, 1990.
- Ron E, Modan B, Preston D, et al.: Thyroid neoplasia following low-dose radiation in childhood. *Radiat Res* 120:516-531, 1989.
- Shore RE, Woodward E, Hildreth N, et al.: Thyroid tumors following thymus irradiation. *J Natl Cancer Inst* 74:1177-1184, 1985.

Occupation

Aaron Blair, Ph.D.*

Industrial workers have long served as sentinels for the general population with regard to environmental hazards. Although many chemicals found in the industrial setting can also be found in the environment, industrial workers often have more intense and prolonged exposures to chemicals than does the general population. Consequently, cancers in humans caused by these substances are often first noted in the workplace.

Many of the well-established and suspected chemical carcinogens were identified through occupational studies. One of the earliest examples occurred more than 200 years ago when, in 1775, Percivall Pott, a London surgeon, described a high frequency of cancer of the scrotum among chimney sweeps, a disease known at the time as "soot-wart." A century later, other scientists noted similar cancers among gas plant workers in Germany and among oil shale workers in Scotland. Some 40 years later, certain constituents of tar, soot, and oils, known as polycyclic aromatic hydrocarbons, were found to cause cancer in laboratory animals, thus identifying the specific substances causing cancer among workers in these occupations. Preventive action was taken in Denmark, where the chimney sweeps' guild, spurred by Pott's report, urged its members to take daily baths. The success of this action was noted in a report in the 1892 *British Medical Journal*, "Why Foreign Sweeps Do Not Suffer From Scrotal Cancer," which pointed out that the sweeps of Northern Europe seemed to benefit from this hygiene measure, but English sweeps, who apparently ignored such recommendations, continued to develop cancer.

This brief detective story became the model for many later investigations of workplace carcinogens, including: observation of unusual cancers, or a high incidence of common cancers, among groups of workers; searches for responsible agents; demonstrations that the agent can cause cancer in laboratory animals; and, finally, implementation of preventive programs.

Studies of occupational groups remain an important component of the current effort to identify the causes of human cancer. A listing and summary of evidence regarding occupational factors that may cause human cancer can be found in a series of critical monographs published by the International Agency for Research on Cancer (IARC). Since 1971, the IARC, an agency of the World Health Organization headquartered in Lyon, France, has published more than 60 volumes dealing with cancer risks from individual chemicals, and mixtures of chemicals, in selected occupations or industries. Individual exposures are reconsidered whenever indicated by new information. The most recent summary of all pertinent reviews was published in 1987 (IARC, Supplement 7).

* From the Occupational Studies Section, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

TABLE 1

Chemicals, Groups of Chemicals, or Industrial Processes Carcinogenic to Humans**GROUP 1:****Industrial processes and occupational exposures that are carcinogenic to humans:**

Aluminum production
 Auramine manufacture
 Boot and shoe manufacture and repair (certain occupations)
 Coal gasification
 Coal-tar pitches
 Coke production
 Furniture manufacture
 Iron and steel founding
 Isopropyl alcohol manufacture (strong-acid process)
 Manufacture of magenta
 Nickel refining
 Rubber industry (certain occupations)
 Underground hematite mining (with exposure to radon)

Chemicals and groups of chemicals that are carcinogenic to humans:

4-Aminobiphenyl
 Arsenic and arsenic compounds
 Asbestos
 Benzene
 Benzdine
 N,N-bis(2-chloroethyl)-2-naphthylamine
 bis(chloromethyl)ether and chloromethyl ethyl ether
 Chromium and certain chromium compounds
 Mineral oils
 Mustard gas
 2-Naphthylamine
 Nickel and nickel compounds
 Soots, tars, and oils
 Vinyl chloride

Occupation

TABLE 2

Chemicals, Groups of Chemicals, or Industrial Processes Probably
or Possibly Carcinogenic to Humans

GROUP 2A:

Probably carcinogenic to humans:

Acrylonitrile
Benzidine-based dyes
Benzo(a)pyrene
Beryllium and beryllium compounds
Cadmium and cadmium compounds
Dimethyl sulphate
Ethylene dibromide
Ethylene oxide
Formaldehyde
Ortho-Toluidine
Polychlorinated biphenyls
Propylene oxide
Silica
Styrene oxide

GROUP 2B:

Possibly carcinogenic to humans:

Acetaldehyde
Acrylamide
Amitrole
Auramine (technical grade)
1,3 Butadiene
Carbon black extracts
Carbon tetrachloride
Chlorophenols
Chlorophenoxy herbicides
DDT
3,3'-Dichlorobenzidine
3,3'-Dimethoxybenzidine (Ortho-Dianisidine)
2,4 Diaminotoluene
1,2 Dichloroethane
Dichloromethane
1,4 Dioxane
Epichlorohydrin
Ethyl acrylate
Ethylene thiourea
Hexachlorobenzene
Hydrazine
Mirex
2-Nitropropane
Organolead
Polybrominated biphenyls
Styrene
Tetrachlorodibenzo-para-dioxin (TCDD)
1,1,2,2 Tetrachloroethane
Tetrachloroethylene
Toluene diisocyanates
Toluidine
Toxaphene
Urethane

Table 3
Cancers Associated with Various Occupations or Occupational Exposures

CANCER	SUBSTANCES OR PROCESSES
Lung	Arsenic, asbestos, bis(chloromethyl)ether, chromium compounds, coal gasification, mustard gas, nickel refining, foundry substances, radon, soots, tars, oils, acrylonitrile, beryllium, silica
Bladder	Aluminum production, auramine and magenta manufacture, rubber industry, leather industry, 4-aminobiphenyl, benzidine, naphthylamine
Nasal cavity and sinuses	Formaldehyde, isopropyl alcohol manufacture, mustard gas, nickel refining, leather dust, wood dust
Larynx	Asbestos, isopropyl alcohol, mustard gas
Pharynx	Formaldehyde, mustard gas
Mesothelioma	Asbestos
Lymphatic and hematopoietic system	Benzene, ethylene oxide, chlorophenols, chlorophenoxy herbicides, X-radiation
Skin	Arsenic, coal tars, mineral oils
Soft-tissue sarcoma	Chlorophenols, chlorophenoxy herbicides
Liver	Arsenic, vinyl chloride

The evaluations in the IARC monographs are based on epidemiologic data from studies in humans, bioassays in animals, and data from short-term tests and laboratory experiments. For the monographs, experts in carcinogenesis evaluate the available data for individual chemicals, chemical groups, industrial processes, or specific occupations and assign each to a category of risk (See Tables 1 and 2). When there is enough evidence from epidemiologic studies to support a causal association with cancer, the chemical, chemical group, process, or exposure is assigned to Group 1 (e.g., asbestos, benzene, chromium, vinyl chloride, coke production, furniture manufacturing, and nickel refining). Chemicals that are carcinogenic in laboratory animals, but for which human data may be limited or lacking, are typically placed in Group 2. Those considered to be probably carcinogenic to humans appear in Group 2A (e.g., acrylonitrile, cadmium, formaldehyde, and silica), and those considered to be possibly carcinogenic to humans are placed in Group 2B (including butadiene, carbon tetrachloride, chlorophenoxy herbicides, DDT, styrene, and tetrachloroethylene). The other categories are considered not classifiable as to carcinogenicity (Group 3), or not carcinogenic to humans (Group 4).

Occupation

The agents carcinogenic to humans (those listed in Table 1) and those probably or possibly carcinogenic to humans (Table 2) do not fall into any particular class of substances. They include metals (arsenic, chromium, nickel, cadmium), solvents (benzene, styrene, carbon tetrachloride, dichloromethane), organic and inorganic dusts (leather or wood dusts, asbestos, silica), chemicals used to construct polymers (acrylonitrile, formaldehyde, vinyl chloride), and pesticides (ethylene oxide, amitrole, chlorophenoxy herbicides, DDT, toxaphene). Tumors in humans associated with occupational exposures from substances or processes listed Tables 1 and 2 are shown in Table 3. Space here is too short for a detailed discussion of each of the agents in Tables 1 and 2 and the tumors they cause, but such information can be found in various reviews, including the IARC Monographs and the Annual Report on Carcinogens by the U.S. Department of Health and Human Services.

Efforts to identify and clarify cancer risks associated with the workplace continue. This research is necessary to ensure a safe work environment and to identify environmental factors that may cause cancer in the general population.

REFERENCES

- IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs 1 to 42, (Suppl 7), Lyon, 1987.
- Seventh Annual Report on Carcinogens: U.S. Department of Health and Human Services, National Toxicology Program, Research Triangle Park, NC, 1994.

Pesticides

Aaron Blair, Ph.D.*

Concern over long-term hazardous effects of pesticides has been a major force behind the environmental movement in the United States, raising serious questions about potential carcinogenic and other toxic effects of these chemicals. The potential for voluntary exposures from agricultural and home use and for involuntary exposures from food residues, water contamination, community and neighbor spraying, or military service has precipitated a major scientific and political controversy.

The evaluation of pesticides for carcinogenicity, which began with animal bioassays in the 1960s (Innes et al., 1969), is now pursued in earnest through a battery of toxicologic and epidemiologic investigations. The National Toxicology Program tested some 50 pesticides in animals, usually using males and females in two species (Ashby and Tennant, 1988). Of these, 17 were positive for carcinogenicity in at least two of the sex/species groups: chlordane, chlordecone, chlorobenzilate, dieldrin, heptachlor, toxaphene, dichlorvos, tetrachlorvinphos, aminotriazole, nitrofen, ozadiazon sulfallate, captan, chlorthalonil, dibromochloropropane, dichloropropane, ethylene dibromide, and ethylene oxide (Blair et al., 1990). An additional six pesticides were positive in one sex in one species: aldrin, dicofol, piperonyl sulphoxide, chloramben, monuron, and trifluralin. The International Agency for Research on Cancer (1987, 1991) has concluded that several pesticides should be considered as probable human carcinogens: amitrole, arsenic, chlordane, chlorophenols, chlorophenoxy herbicides, DDT, 1,2-dibromochloropropane, ethylene dibromide, ethylene oxide, Mirex, and toxaphene.

Studies of human populations exposed to pesticides are also available (Blair et al., 1990). Many of these studies evaluated cancer risks from use of pesticides in general, without attempting to focus on specific chemicals. For example, excesses of lung cancer have been observed in some studies of agricultural (Barthel, 1981) and urban applicators (Blair et al., 1983, MacMahon, 1988), but these excesses could not be related to individual pesticides. Surveys in a number of developed countries have noted excesses for several cancers among farmers, including leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the skin, lip, stomach, brain, and prostate (Blair et al., 1992). Farmers represent an occupation that may have frequent contact with a variety of pesticides, which underscores the need for additional investigations of agricultural populations.

A few recent epidemiologic studies have attempted to evaluate specific pesticides. Lung cancer has been associated with blood levels of DDT among residents of South Carolina (Austin et al., 1989), and pancreatic cancer risk was excessive among workers employed in the manufacture of DDT (Garabrant et al., 1992).

Levels of DDT and its metabolites in blood and adipose tissue have been associated with breast cancer in recent studies in the United States (Falck et al., 1992; Wolff et al., 1993; Krieger et al., 1994). These epidemiologic findings, coupled with experi-

* From the Occupational Studies Section, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Pesticides

mental evidence of the carcinogenicity of DDT in laboratory animals, suggest that this pesticide may present a cancer hazard to humans.

Increased risks for several lymphatic and hematopoietic cancers have been found among individuals exposed to insecticides in the United States (Hoar et al., 1986; Boffetta et al., 1989; Cantor et al., 1992; Zahm et al., 1990; Brown et al., 1990), Sweden (Flodin et al., 1988), and Italy (Corrao et al., 1989). Several groups of pesticides may be involved, including organochlorines, organophosphates, and carbamates, but additional research is necessary to determine definitively which—if any—are human carcinogens.

Epidemiologic investigations have also linked herbicides with some cancers. Phenoxycetic acid herbicides have been associated with non-Hodgkin's lymphoma in Sweden (Hardell et al., 1981; Persson et al., 1989), Canada (Wigle et al., 1990), and the United States (Hoar et al., 1986; Zahm et al., 1990) and with soft-tissue sarcomas in Sweden (Hardell et al., 1979; Eriksson et al., 1981), Denmark (Lynge, 1985), and Italy (Vineis et al., 1987). Studies in New Zealand, however, did not find such associations (Smith and Pearce, 1986; Pearce, 1989). Use of phenoxycetic acid herbicides on lawns was also associated with malignant lymphoma in dogs (Hayes et al., 1991). There is no clear evidence from bioassays, however, that phenoxycetic acid herbicides cause cancer in animals. Concerns have recently been raised about triazine herbicides, another widely used group of weed killers. Some triazine herbicides cause breast cancer in rodents (IARC, 1992) and have been associated with ovarian cancer among Italian women engaged in agricultural activities (Donna et al., 1989). A study of manufacturers of phenoxycetic acid herbicides exposed to dioxin showed they experienced excesses for several cancers, including lung cancer, and soft-tissue sarcoma (Fingerhut et al., 1991).

Experimental data indicate that several pesticides can cause cancer in animals, thus raising concerns about human exposures. Epidemiologic studies suggest that occupational exposure to some pesticides may present a carcinogenic hazard. Although evidence that pesticides cause cancer in humans is not conclusive, a prudent course would be to minimize exposure through use of protective practices and appropriate personal hygiene. Research is continuing to clarify cancer risks from specific pesticides and to determine mechanisms of action.

REFERENCES

- Ashby J, Tennant RW: Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. *Mutation Research* 204:17-115, 1988.
- Austin H, Keil JE and Cole P: A prospective follow-up study of cancer mortality in relation to serum DDT. *Am J Public Health* 79:43-46, 1989.
- Barthel E: Increased risk of lung cancer in pesticide-exposed male agricultural workers. *J Toxicol Environ Health* 8:1027-1040, 1981.
- Blair A, Axelsson O, Franklin C, et al.: Carcinogenic effects of pesticides. In *The Effect of Pesticides on Human Health* (Baker SR, Wilkinson CF, eds.). *Adv Modern Environ Toxicol* 8:201-260, Princeton Scient. Publ. Co., 1990.
- Blair A, Grauman DJ, Lubin JH, et al.: Lung cancer and other causes of death among licensed pesticide applicators. *J Natl Cancer Inst* 71:31-37, 1983.
- Blair A, Zahm SH, Pearce NE, et al.: Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 18:209-215, 1992.
- Boffetta P, Stellman SD and Garfinkel L: A case-control study of multiple myeloma nested in the American Cancer Society prospective study. *Int J Cancer* 43:554-559, 1989.
- Brown LM, Blair A, Gibson R, et al.: Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res* 50:6585-6591, 1990.
- Cantor KP, Blair A, Everett G, et al.: Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 52:2447-2455, 1992.
- Corrao G, Galleri M, Carle F, et al.: Cancer risk in a cohort of licensed pesticide users. *Scand J Work Environ Health* 15:203-209, 1989.
- Donna A, Crosignani P, Robutti F, et al.: Triazine herbicides and ovarian neoplasms. *Scand J Work Environ Health* 15:47-53, 1989.
- Eriksson M, Hardell L, Berg NO, et al.: Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. *Br J Ind Med* 38:27-33, 1981.
- Falck F, Ricci A, Wolff MS, et al.: Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health* 47:143-146, 1992.
- Fingerhut MA, Halperin WE, Marlow DA, et al.: Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *New Engl J Med* 324:212-218, 1991.
- Garabrant DH, Held J, Langholz B, et al.: DDT and related compounds and risk of pancreatic cancer. *J Natl Cancer Inst* 84:764-771, 1992.
- Hardell L, Eriksson M, Lenner P, et al.: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols, and phenoxy acids: A case-control study. *Br J Cancer* 43:169-176, 1981.
- Hardell L and Sandstrom A: Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer* 39:711-717, 1979.
- Hayes HM, Tarone RE, Cantor KP, et al.: Case-control of canine malignant lymphoma: Positive association with dog owner's use of 2,4-dichlorophenoxyacetic acid herbicides. *J Natl Cancer Inst* 83:1226-1231, 1991.
- Hoar SK, Blair A, Holmes FF, et al.: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 256:1141-1147, 1986.
- International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs 1 to 42. (Suppl 7), Lyon, 1987.
- International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Occupational Exposures in Insecticide Application and Some Pesticides, vol. 53. Lyon, 1987.
- Innes JRM, Ulland BM, Valeria MG, et al.: Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J Natl Cancer Inst* 42:1101-1114, 1969.
- Krieger N, Wolff MS, Hiatt RA, et al.: Breast cancer and serum organochlorines: A prospective study among white, black, and Asian women. *J Natl Cancer Inst* 86:589-599, 1994.

- Lynge E: A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer* 52: 259-270, 1985.
- MacMahon B, Monson RR, Wang HH, et al.: A second follow-up of mortality in a cohort of pesticide applicators. *J Occup Med* 30:429-432, 1988.
- Pearce N: Phenoxy herbicides and non-Hodgkin's lymphoma in New Zealand: Frequency and duration of herbicide use. *Br J Ind Med* 46:143-144, 1989.
- Persson BA, Dahlander A, Fredrickson M, et al.: Malignant lymphomas and occupational exposures. *Br J Ind Med* 46:516-520, 1989.
- Smith AH and Pearce NE: Update on soft-tissue sarcoma and phenoxyherbicides in New Zealand. *Chemosphere* 15:1795-1798, 1986.
- Vincis P, Terracini B, et al.: Phenoxy herbicides and soft-tissue sarcomas in female rice weeder. *Scand J Work Environ Health* 13:9-17, 1987.
- Wigle DT, Semenciw RM, Wilkins K, et al.: Mortality study of Canadian male farm operators: Non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 82:575-582, 1990.
- Wolff MS, Toniolo PG, Lee E, et al.: Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst* 85:648-652, 1993.
- Zahn SH, Weisenburger DD, Babbitt PA, et al.: A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1:349-356, 1990.

Solar radiation exposure is the chief cause of nonmelanoma (i.e., basal cell and squamous cell) skin cancer. It is also a prime factor in the etiology of cutaneous melanoma (Armstrong, 1994).

Nonmelanoma skin cancers are now considered to be over 99 percent curable. Though they accounted for as many deaths in the United States during the 1950s and 1960s as did melanomas, which are rarer but far more lethal (Ries, 1990; Riggan et al., 1983), mortality rates decreased in the 1970s while melanoma death rates increased. Currently, more than 600,000 new cases of nonmelanoma skin cancer are thought to occur in the United States each year, and this number is rising. With an annual rate equal to about half the rate observed for all other cancers combined, nonmelanoma skin cancer is the most common form of cancer among Caucasians. In the South, the incidence of skin cancer exceeds that of all other cancers combined, and in parts of the North it accounts for about 30 to 40 percent of all cancers (Scotto, 1983).

The relationship between sun exposure and nonmelanoma skin cancer has been clarified greatly in the past several decades (Blum, 1959; Emmett, 1973; Urbach, 1974; Kricker et al., 1994). Observers noted in the late 1800s (Unna, 1894) that sailors exposed to the sun developed "Seemannshaut," or "sailor's skin," and in the early 1900s an excess risk of skin cancer was observed among farmers. The greater risk for Caucasians exposed to sun was also observed (Hyde, 1906).

By 1928, scientists were able to demonstrate the cancer-causing effects of ultraviolet radiation on the skin of laboratory animals, using both sunlight and artificial light sources (Findlay, 1928). These carcinogenic effects were produced by ultraviolet-B (UV-B) radiation in the 290- to 320-nanometer (nm) range—the same range that produces burning in human skin (erythema). UV-B exposure can alter DNA, and may also affect the immunosuppressive system (Kripke, 1990).

Though latitude, or distance from the equator, generally determines the amount of UV-B radiation in a given location, altitude and sky cover are also determining factors. Atlanta, Georgia, and El Paso, Texas, for example, are in the same general latitude (32 to 33°N). But El Paso, which is higher and drier, has an annual UV-B count 38 percent higher than Atlanta. The amount of UV-B received annually in Hawaii (at about 19°N) is approximately 10 times that received in Alaska (at about 72°N).

Time of day and time of year also affect the amount of UV-B radiation in any location. The greatest amount, of course, occurs during the summer months, and 60 percent of the day's total amount occurs between the hours of 10 a.m. and 2 p.m.

Solar Radiation

Joseph Scotto, M.S.*

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Solar Radiation

(or 3 p.m. DST). The safest time of day to be outdoors is when the sun's angle is less than 45° above the horizon. As a rule of thumb, this occurs when a person's shadow is longer than his or her height.

In 1974, Robertson-Berger (Berger, 1975) designed meters to measure surface levels of UV-B radiation. In collaboration with the NCI, the National Oceanic and Atmospheric Administration (NOAA) placed these meters at a number of National Weather Service stations in the United States. Physical data from these meters, combined with epidemiological data from NCI surveys, allowed scientists for the first time to use direct measurements of ambient UV-B to estimate the potential health effects associated with solar radiation exposure (Scotto, 1976). The most striking association was the inverse relationship between latitude and non-melanoma skin cancer: The lower the latitude (the equator is zero), the higher the incidence. The data also indicated that nonmelanoma skin cancer is related to annual, cumulative UV-B exposure, while skin melanoma may be related to brief exposure to high-intensity UV radiation (Fears, 1977). A 1 percent increase in solar UV-B exposure may result in a 2 percent increase in the incidence rate of basal cell carcinoma, a 4 percent increase in squamous cell carcinoma of the skin, and a 1 percent increase in skin melanoma (Scotto, 1976, 1983; Fears, 1977; Rundel 1983; Green, 1978). Subsequent NCI studies have confirmed initial dose-response findings for both melanoma and nonmelanoma of the skin (Scotto et al., 1982; Scotto and Fears, 1987).

The single most important factor affecting UV-B exposure is the amount of ozone (O_3) in the atmosphere (Cutchis, 1974). Ozone gases absorb most of the UV light in the upper stratosphere and allow only small amounts (less than .1 percent) to reach the earth's surface. There has been growing concern since the early 1970s (Roan, 1990) that man-made chlorofluorocarbons (CFCs such as aerosol propellants, refrigerants, solvents for computer chips, and insulation in styrofoam containers) are destroying ozone molecules in the stratosphere and may have caused the recent "Ozone Hole" (Farman et al., 1985) over parts of Antarctica. Current estimates predict that ozone concentration could be reduced by 6 percent or more within several decades if world levels of CFC production continue. Many nations have signed an agreement, called the Montreal Protocol, which would limit and possibly end CFC production by the year 2000.

Solar Radiation

As much as a 2 percent increase in UV-B radiation may be expected for each 1 percent reduction in stratospheric ozone concentration. These concerns are now being studied by a number of federal agencies. However, though stratospheric ozone reportedly decreased between 1969 and 1987 (WMO, 1989), with highest depletion rates occurring during the winter months when UV-B levels are lowest, no increases in the annual amounts of biologically effective solar ultraviolet radiation at the earth's surface were observed between 1974 and 1985 in the United States (Scotto, 1988).

Solar radiation exposure ranks high among the "lifestyle" factors associated with skin cancers. Most individuals have some choice in the amount of sunlight exposure they receive. Preventive measures (e.g., using sunscreens and protective clothing, and avoiding sunlight exposure around the noontime hours) may outweigh the effects of small relative decreases in stratospheric ozone.

REFERENCES

- Armstrong BK: Stratospheric ozone and health. *Int J Epidemiol* 23:873-885, 1994.
- Berger D, Robertson DE, et al.: Field measurements of biologically effective UV radiation. In *Impacts of Climatic Change of the Biosphere*. CLAP Monograph 5, Department of Transportation DOT-TST-75-55, Springfield, VA NTIS: 2-235 to 2-263, 1975.
- Blum H: *Carcinogenesis by Ultraviolet Light*. Princeton, NJ: Princeton University Press, 1959.
- Catchis P: Stratospheric ozone depletion and solar ultraviolet radiation on earth. *Science* 184:13-19, 1974.
- Emmett EA: Ultraviolet radiation as a cause of skin tumors. *CRC Crit Rev Toxicol* 2:211-255, 1973.
- Farman JC, Gardiner BG and Shanklin JD: Large losses of total ozone in Antarctica reveal seasonal ClOx/NOx interaction. *Nature* 315:207-210, 1985.
- Fears TR, Scotto J and Schneiderman MA: Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. *Am J Epidemiol* 105:120-127, 1977.
- Findley GM: Ultraviolet light and skin cancer. *Lancet* 2:1070-1073, 1928.
- Hyde JN: On the influence of light in the production of skin cancer. *Am J Med Sci* 131:1-22, 1906.
- Green AFS and Hedinger RA: Models relating ultraviolet light and nonmelanoma skin cancer incidence. *Photochem Photobiol* 28:283-291, 1978.
- Kricker A, Armstrong BK and English DR: Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* 5:367-392, 1994.
- Kripke ML: Effects of UV radiation on tumor immunity. *J Natl Cancer Inst* 82, No 17:1392-1396, 1990.
- Ries LAG, Hankey BF and Edwards BK: Cancer statistics review, 1973-87. NHH Publ. 90-2789, U.S. Department of Health and Human Services, Washington, DC, 1990.
- Riggan WB, Van Bruggen J, Acquavella JE, et al.: US cancer mortality rates and trends, 1950-1979. U.S. EPA, EPA-600/1-83-015a, 1983.
- Roan S: *Ozone Crisis, The 15-year Evolution of a Sudden Global Emergency*. New York: Wiley & Sons Inc., 1990.
- Rundel RD and Nachtwey DS: Projections of increased non-melanoma skin cancer incidence due to ozone depletion. *Photochem Photobiol* (38):18(5):577-591, 1983.
- Scotto J, Fears TR and Fraumeni JF Jr: Solar radiation, pp. 254-276. In *Cancer Epidemiology and Prevention*. (Schottenfeld D, Fraumeni JF Jr, eds.) Philadelphia: W.B. Saunders Company, 1982.
- Scotto J and Fears TR: The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States. *Cancer Invest* 5(1):275-283, 1987.
- Scotto J, Fears TR and Gori GB: Measurements of Ultraviolet Radiation in the United States and Comparison with Skin Cancer Data. DHEW (NIH) 76-1029. Bethesda, MD: National Cancer Institute, 1976.
- Scotto J, Fears TR and Fraumeni JF, Jr: Incidence of Nonmelanoma Skin Cancer in the United States. NCI NIH Publ. No. 83-2433, 1983.
- Scotto J, Cotton G, Urbach F, et al.: Biologically effective ultraviolet radiation: Surface measurements in the United States, 1974 to 1985. *Science* 239:762-764, 1988.
- Umma PG: *Die Histopathologie der Hauptkrankheiten*. Berlin: August Hirschwald, 1894.
- Urbach F, Epstein JH and Forbes PD: Ultraviolet carcinogenesis: Experimental, global and genetic aspects, pp. 259-283. In *Sunlight and Man: Normal and Abnormal Photobiologic Responses*. (Fitzpatrick TB, Pathak MA, Harber LS, et al., eds.). Tokyo: Univ. of Tokyo Press, 1974.
- World Meteorological Organization (WMO): Global Ozone Research and Monitoring Project—Report No. 20, Scientific assessment of stratospheric ozone. NASA, 1989.

The concept that viruses cause human cancer dates back to the first decade of the 20th century, when experiments on animals showed that tumors could be induced in chickens by an agent that could pass through a filter. This pioneering work by Francis Peyton Rous in the United States was recognized more than 50 years later with the 1972 Nobel Prize that he shared with Howard Temin and David Baltimore, who characterized the molecular biology of retroviruses, first detected in Rous's experiments. Over the last decade, the new tools of molecular biology have led to profound discoveries about the role of viruses in human cancer and the mechanisms of disease causation.

Viruses are a type of infectious agent that must invade living cells in order to reproduce. The two major types of viruses have either DNA or RNA as their genetic material. Viruses often invade cells by attaching to receptors on the surface of the target cell. Once inside the cell, they often integrate their genetic material into that of the host and alter the cell in ways that predispose to cancer through a variety of mechanisms. In some cases, the virus is thought to induce cancer directly; in other cases, indirect effects of the virus (e.g., immunodeficiency) predispose to malignancy. The major classes of viruses that are linked to cancer are retroviruses, herpes viruses, papilloma viruses, hepadnaviruses (hepatitis B), and flavaviruses (hepatitis C) (Evans and Mueller, 1990). In addition, genes called oncogenes, first discovered as part of the genetic material of acutely transforming retroviruses but now recognized as part of the normal genetic makeup of the cell, have been identified as critical factors in the oncogenic process.

The first human retrovirus, discovered by Robert C. Gallo of the National Cancer Institute, is called human lymphotropic virus type I (HTLV-I) (Blattner, 1990). This prototype human retrovirus is strongly associated with malignant lymphomas of T-lymphocytes, first recognized in Southern Japan and called adult T-cell leukemia/lymphoma. A characteristic feature of these tumors is the monoclonal integration of the viral genome in the tumor tissue. Because the leukemia may occur years to decades after infection—which often occurs at birth—it is hypothesized that other factors play a role in pathogenesis. However, viral genes have the capacity to turn on genes of the host cell, promoting cell growth that may lead to uncontrolled cell proliferation. Recently, HTLV-I has been linked to a chronic neurologic syndrome called HTLV-associated myelopathy, which, because of demyelination, bears some resemblance to multiple sclerosis. The HTLV-I virus also causes a pediatric immunodeficiency syndrome called infective dermatitis and adult autoimmune diseases such as polymyositis and arthritis. Because of these immunologic effects of HTLV-I, it has been hypothesized that some more common cancers might be enhanced by HTLV-I infection through indirect mechanisms such as immunodeficiency. The closely related HTLV-II virus has not been definitively linked to can-

Viruses, Retroviruses, and Associated Malignancies

William A. Blattner, M.D.*

* From the Viral Epidemiology Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Viruses, Retroviruses, and Associated Malignancies

cer, although it was first isolated from a patient with a rare form of T-lymphocyte leukemia. The recent discovery that HTLV-II occurs naturally among some native American populations has created new opportunities to determine whether this "orphan" virus contributes in any way to cancer or other disease causation (Blattner, 1993). Since 1990, the American blood supply has been screened for HTLV-I. As a consequence, numerous donors have been identified as seropositive and have sought counseling concerning the health implications of this infection. While disease risk is not fully characterized, experts agree that the risk of leukemia and other complications is low, with an estimated lifetime risk of approximately 3 to 5 percent for an HTLV-associated disease (Blattner, 1993).

The emergence of an epidemic of Kaposi's sarcoma in the United States among gay men, first recognized in 1981, was soon linked to the epidemic of acquired immunodeficiency syndrome, and an infectious agent postulated. The techniques pioneered by Robert C. Gallo were critical to the isolation of human immunodeficiency virus by Gallo and Luc Montagnier of The Institut Pasteur in Paris. This class of virus has as its major effect the induction of profound immunodeficiency through its ability to infect T-lymphocytes and cause their destruction (Blattner, 1991). While the process of HIV-associated immunodeficiency is complex, including direct killing effects of the virus on T-lymphocytes, lymphokine-mediated immune perturbations, and "autoimmune" mechanisms, the end result is a progressive depletion of CD-4 positive T-helper lymphocytes. This depletion results in heightened susceptibility of the infected individual to a variety of "opportunistic" pathogens as well as numerous cancers.

Kaposi's sarcoma is a cancer of the lining of blood vessels which can occur on the skin, or be more widely disseminated in vital organs. Before the AIDS-associated epidemic, Kaposi's sarcoma was a rare tumor reported largely among older men, often of Mediterranean ancestry, and in residents of central Africa. The epidemic form is largely seen among gay men and is much more rare in other groups at risk of HIV infection. Some epidemiologic data suggest that an infectious agent may be involved and studies are under way to search for such an agent (Beral et al., 1990). Recently, a novel herpesvirus has been implicated in the pathogenesis of AIDS-related body-cavity-based lymphomas (Cesarman et al., 1995). The other major tumor type is non-Hodgkin's lymphoma, which occurs in all risk groups and appears strongly related to profound immunodeficiency (Rabkin et al., 1991).

The pattern of tumor types and the high frequency of lymphomas of the central nervous system mirror the pattern of lymphomas associated with congenital and transplantation-associated immunosuppression (MacMahon et al., 1991). In one recent analysis, it was estimated that between 8 percent and 10 percent and up to 25 percent of all lymphomas in the United States will be AIDS-associated in coming

years (Gail et al, 1991). Molecular studies have suggested that these lymphomas are linked to the Epstein-Barr virus (EBV), often with the pattern of oncogene translocation associated with Burkitt's lymphoma, which is a type of virally associated cancer originally described by Sir Dennis Burkitt in the 1960s. Thus, AIDS-associated cancers may represent examples of a process of immunosuppression allowing other oncogenic viruses such as EBV or the more recently discovered human herpes virus 6 (HHV-6) to be expressed as cancer (Cohen, 1991).

It is likely that some other virally-associated cancers will show increases among HIV-positive immunosuppressed persons. For example, preliminary data suggest that human papilloma viruses may be increased in HIV-infected persons, with the potential for enhancing induction of associated tumors.

As noted above, Epstein-Barr virus has been linked to Burkitt's lymphoma as well as other lymphomas, Hodgkin's disease (Herbst et al., 1991), and nasopharyngeal carcinoma (Litter, 1991). Intervention studies with an EBV vaccine are now under way in hopes of preventing some of these cancer types.

Worldwide, hepatocellular carcinoma is a leading cause of death. A role for hepatitis B in the etiology of this tumor is well established (Blumberg and London, 1982). For example, very large studies of persons from populations where hepatitis B is frequent have shown an exceptional risk for cancer among antigen carriers who have not developed an adequate antibody response to the virus (Paterlini et al., 1990). Vaccine trials are also under way with this virus in order to prevent infections and associated hepatocellular cancer. The recently discovered hepatitis C, has also been linked to hepatocellular carcinoma (Simonetti et al., 1992). Given the very different nature of these two viruses, important clues about the role of viruses that cause liver damage and cancer will emerge as more is learned.

The decade of the 1990s is exciting because of the advances in techniques for detecting and characterizing oncogenic viruses. It is likely that new agents that cause cancer will be discovered, and cancers of unknown cause linked to known and yet to be discovered agents.

Viruses, Retroviruses, and Associated Malignancies

REFERENCES

- Beral V, Peterman TA, Berkelman RL, et al.: Kaposi's sarcoma among persons with AIDS: A sexually transmitted infection. *Lancet* 335:123-128, 1990.
- Blattner W: Epidemiology of HTLV-I and associated diseases. (Blattner W, ed.). In *Human Retrovirology: HTLV*. New York: Raven Press, 1990, 251-265.
- Blattner W: HIV epidemiology: past, present, and future. *FASEB J* 5:2340-2348, 1991.
- Blattner W: Human T-cell lymphotropic viruses and cancer causation. In *Cancer Prevention*. (DeVita VT Jr, Hellman S and Rosenberg SA, eds.). Philadelphia: J.B. Lippincott Co., 1993.
- Blumberg BS and London WT: Hepatitis B virus: Pathogenesis and prevention of primary cancer of the liver. *Cancer* 50:2657-2665, 1982.
- Cesarman E, Chang Y, Moore PS, et al.: Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS related body-cavity-based lymphomas. *N Engl J Med* 332:1186-1191, 1995.
- Cohen JL: Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. *Medicine* 70(2):137-160, 1991.
- Evans AS and Mueller NE: Viruses and Cancer: Causal associations. *Ann Epidemiol* 1(1):71-92, 1990.
- Gail MH, Pluda JM, Rabkin CS, et al.: Projections of the incidence of non-Hodgkin's lymphoma related to acquired immunodeficiency syndrome. *J Natl Cancer Inst* 83(10):695-701, 1991.
- Herbst H, Dallenbach F, Hummel M, et al.: Epstein-Barr virus latent membrane protein expression in Hodgkin and Reed-Sternberg cells. *Proc Natl Acad Sci USA* 88:1766-1770, 1991.
- Latter E, Baylis SA, Zeng Y, et al.: Diagnosis of nasopharyngeal carcinoma by means of recombinant Epstein-Barr virus proteins. *Lancet* 337 (8743):685-689, 1991.
- MacMahon FME, Glass JD, Hayward SD, et al.: Epstein-Barr virus in AIDS-related primary central nervous system lymphoma. *Lancet* 338:969-973, 1991.
- Paterlini P, Gerken G, Nakamura E, et al.: Polymerase chain reaction to detect hepatitis B virus DNA and RNA sequences in primary liver cancers from patients negative for hepatitis B surface antigen. *N Engl J Med* 323:80-85, 1990.
- Rabkin CS, Biggar RJ and Horn JW: Increasing incidence of cancers associated with the human immunodeficiency virus epidemic. *Int J Cancer* 47:692-696, 1991.
- Simonetti RG, Camma C, Fiorello F, et al.: Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. *Ann Int Med* 116:97-102, 1992.

Biliary Tract

Joseph McLaughlin, Ph.D.*

Little is known about the etiology of biliary tract cancer, which includes cancers of the gallbladder and extrahepatic bile ducts. In general, these cancers are more common outside the United States in areas such as South America and Eastern and Central Europe (Whelan et al., 1990; Fraumeni and Kantor, 1982). Within the United States, American Indians and Hispanic Americans are at greater risk than the general population, particularly for gallbladder cancer (Diehl, 1980; Fraumeni and Kantor, 1982).

Gallbladder Cancer

Although rare, cancer of the gallbladder is more likely to occur among women than men. The incidence per 100,000 population, during the period 1975-1985, was 1.7 for white women and 0.9 for white men. Rates for whites and blacks were similar, but the rates for American Indians were highest (17.1 for men, 8.8 for women). Gallbladder cancer was also elevated among Hispanic Americans, with women having a rate of 7.3, and men, 1.7. The incidence rate for gallbladder cancer in both sexes has declined slightly since the late 1960s, which may be due in part to the large number of cholecystectomies (surgery to remove the gallbladder) performed each year in the United States (Graves, 1991). Survivorship of patients with this cancer is poor, with less than 10 percent living more than five years after diagnosis.

Gallstones are by far the most important risk factor for gallbladder cancer. Stones are reported in 60 to 80 percent of patients with gallbladder cancer, although the cancer itself occurs in only a very small fraction of the millions of individuals with gallstones (Bennion and Grundy, 1978; Fraumeni and Kantor, 1982). American Indians and Hispanic Americans also have a high rate of gallstones. Presumably, controlling the formation of gallstones would reduce the number of individuals with gallbladder cancer. Factors related to stone formation are: increasing age, being a woman, increased number of children, ethnicity, obesity, use of estrogen-containing drugs, and high fat and caloric intake (Bennion and Grundy, 1978; Diehl, 1980). A recent study, however, did not find oral contraceptive users to be at increased risk for gallbladder cancer (WHO Collaborative Study, 1989). A few studies have linked occupational factors with gallbladder cancer, including employment in rubber and automobile plants, papermills, petroleum refineries, and clothing factories, but it is uncertain whether these associations are causal (Malker et al., 1986).

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Biliary Tract

Other Biliary Tract Cancers

Extrahepatic bile duct cancer is the primary tumor included among "other biliary tract cancers." Men predominate in this uncommon cancer, with an incidence rate among whites of 1.5 for men compared with 1.0 for women. As with gallbladder cancer, there is little difference in occurrence between whites and blacks.

American Indians, however, have higher rates (4.2 for men, 2.8 for women). Japanese- and Chinese-Americans also have higher rates than whites or blacks, but lower rates than American Indians. Incidence rates for other biliary tract cancers have not changed appreciably in the last 20 years. As with gallbladder cancer, patients survive poorly, with only about 10 percent still alive five years after diagnosis.

Aside from gallstones, which occur in about 30 percent of patients with extrahepatic bile duct tumors, risks factors are few (Fraumeni and Kantor, 1982; Yen et al., 1987). The male excess might suggest cigarette smoking as a factor, but the one study that examined this issue found no excess risk (Yen et al., 1987). Other possible risk factors include ulcerative colitis; infestation with liver flukes; use of methyldopa (an antihypertensive agent); exposure to asbestos; employment in aircraft, chemical, and rubber plants; and use of oral contraceptives (Yen et al., 1987; Malher et al., 1986). None of these associations, however, has been solidly confirmed by well-designed epidemiologic studies.

REFERENCES

- Bennion LJ and Grundy SM: Risk factors for the development of cholelithiasis in man. *N Engl J Med* 299:1161-1167, 1221-1227, 1978.
- Diehl AK: Epidemiology of gallbladder cancer. A synthesis of recent data. *J Natl Cancer Inst* 65:1209-1214, 1980.
- Fraumeni JF Jr and Kantor AR: Biliary tract. In *Cancer Epidemiology and Prevention*. (Schottenfeld D, Fraumeni JF Jr, eds). Philadelphia: WB Saunders, 1982.
- Graves EJ: 1989 Summary: National hospital discharge survey. *Advance Data*: Vol. 199, April 4, 1-11, 1991.
- Malker HS, McLaughlin JK, Malker BK, et al.: Biliary tract cancer and occupation in Sweden. *Br J Ind Med* 43:257-262, 1986.
- Whelan SL, Parkin DM and Masuyer E: Patterns of cancer in five continents. Lyon, France: International Agency for Research on Cancer, IARC Sci Publ No. 102; 30, 1990.
- WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Combined oral contraceptives and gallbladder cancer. *Int J Epidemiol* 18:309-314, 1989.
- Yen S, Hsieh CC and MacMahon B: Extrahepatic bile duct cancer and smoking, beverage consumption, past medical history, and oral contraceptive use. *Cancer* 59:2112-2116, 1987.

Brain and Other Nervous System

Terry L. Thomas, Ph.D.,* and
Peter D. Inskip, Sc.D.**

The nervous system consists of two parts: (1) the central nervous system (CNS), which includes the brain and spinal cord, and (2) the peripheral nervous system. Tumors arise in both parts of the nervous system, but nine out of 10 nervous system cancers occur in or around the brain. Most tumors develop from glial cells, which form supporting structures for nerve cells; tumors originating in nerve cells are rare. "Glioma" is a general term that includes any tumor arising from glial cells. Examples include astrocytic tumors (astrocytoma and glioblastoma multiforme), ependymoma, and oligodendroglioma.

The different types of brain and other nervous system tumors occur with different relative frequencies among children and adults (Schoenberg et al., 1976). The most common tumors of childhood are astrocytic tumors and a group of cancers known collectively as primitive neuroectodermal tumors, of which the most common types are medulloblastoma and neuroblastoma of the CNS (Rorke, 1983). Among adults, the most frequent types are astrocytic tumors, meningioma, acoustic neuroma, and pituitary gland tumors. In general, astrocytic tumors occurring among adults are more malignant and carry a graver prognosis than those seen among children. Meningiomas arise from cells in the membranes that surround the brain and spinal cord. Other types of nervous system tumors include neurofibroma (Schwannoma), neurofibrosarcoma, retinoblastoma, and tumors of the pineal gland. Many nervous system tumors are benign; that is, they do not invade other parts of the body. However, even benign and slow-growing tumors of the nervous system can produce serious neurologic symptoms. The skull has no flexibility to accommodate a growing tumor mass, so as tumors grow, they exert pressure on neighboring nerve tissue.

Brain cancers usually do not spread outside the central nervous system, but cancers from other sites frequently spread, or metastasize, to the central nervous system (Schoenberg, 1982). Breast cancer, for example, often metastasizes to the brain and spinal cord. Melanoma and cancers of the lung, kidney, and gastrointestinal tract also sometimes metastasize to the brain. These tumors are not considered to be primary tumors of the nervous system, because they originate in other parts of the body; therefore, the rest of this chapter concerns only tumors that originate in the nervous system.

There is a small peak in the age-incidence of brain and nervous system cancer under the age of 10—when brain cancer is the second most common cancer—and a much larger peak among adults in the eighth decade of life. The apparent decrease in incidence past the age of 80 is probably indicative of a less aggressive diagnostic approach with patients of very advanced age (Annegers, 1981; Schoenberg, 1978).

* From the Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland

** From the Radiation Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Brain and Other Nervous System

Incidence rates for brain and other nervous system cancers vary with sex, race, and country as well as with age. In the United States, the annual incidence rate for brain and other nervous system cancers is about 7.4 cases per 100,000 population among men, and 5.3 among women (standardized to the age distribution of the 1970 U.S. population) (Ries et al., 1994). The corresponding annual death rates are 5.1 for men and 3.5 for women. Gliomas are more common among males, but meningiomas are more common among females, which suggests the possibility of hormonal factors in the development of one or both of these types of tumor.

In the United States, nervous system cancers occur more often among whites than blacks, and least often among persons of Asian background (Parkin et al., 1992). The incidence of nervous system cancers among whites is about 7.9 cases per 100,000 population among men and 5.7 among women (1970 standard). The incidence rate of nervous system cancers among black men is 4.7 per 100,000 population and among black women is 3.3 (Ries et al., 1994). Whites develop gliomas at a higher rate than do blacks, whereas blacks are more likely to develop meningiomas (Heshmat et al., 1976; Preston-Martin, 1989).

Internationally, the highest rates of brain and nervous system cancer are seen in Scandinavian countries and Israel, while low rates are reported for Asian countries (Parkin et al., 1992). Interpretation of variations in brain cancer rates among cancer registries from different countries is uncertain, because of inconsistencies in the completeness of ascertainment, in methods of reporting, and in limitations in the diagnostic methods available to distinguish primary from metastatic tumors.

Similar issues complicate the interpretation of trends in brain cancer rates over time. Incidence rates for brain cancer have increased by 25 percent since 1973, at an annual rate of 1.2 percent, while mortality has increased by 16 percent (Ries et al., 1994). Examination of changes in age-specific rates shows the increase in both incidence and mortality to be especially pronounced among older persons (Ries et al., 1994). This is almost certainly due, in large part, to improved detection of brain tumors among the elderly. Technological advances have made it easier to detect brain tumors without having to do a biopsy. Tumors among the elderly that might previously have been missed or misdiagnosed are now being ascertained. However, the possibility cannot be ruled out that a small part of the apparent increase in the incidence rate is real and indicative of increased exposure to environmental neurocarcinogens.

The causes of tumors of the brain and nervous system are largely unknown, but genetic factors and a variety of environmental factors have been implicated to varying degrees. Certain inherited syndromes, such as neurofibromatosis, predispose persons to develop tumors of the nervous system, but such syndromes are rare.

Brain and Other Nervous System

Persons who inherit an altered form of a particular gene are at greatly increased risk of developing retinoblastoma. Parents and siblings of children with brain cancer appear to have a slightly increased risk of developing a brain tumor (Kuijten et al., 1990, 1993).

Epidemiologic studies have linked nervous system cancers with a variety of environmental exposures, including physical, chemical, and biologic agents (Preston-Martin et al., 1989; Kuijten and Bunin, 1993). Two categories of environmental exposure that have attracted considerable interest in recent years as possible causes of nervous system tumors in humans include electromagnetic fields and a family of chemicals known as N-nitroso compounds. Interest in the latter was prompted by the observation that alkyl nitrosoureas, one category of N-nitroso compound, are the most potent neurocarcinogens yet identified in experimental studies with laboratory animals (Kleihues et al., 1976; Magee 1976). Humans are exposed to N-nitroso compounds through a variety of avenues, including diet; use of alcohol and tobacco; certain medications, cosmetics, and lotions; and through their jobs (Preston-Martin and Henderson, 1984). However, results of studies concerning N-nitroso compounds and brain tumors in humans are highly inconsistent (Preston-Martin et al., 1982; Howe et al., 1989; Kuijten et al., 1990; Bunin et al., 1993, 1994a,b; Sarasua and Savitz, 1994). With regard to other dietary factors, some information indicates that consumption of fruits and vegetables and of vitamins C and E might protect against the occurrence of brain tumors (Burch et al., 1987; Bunin et al., 1993).

Cancers of the brain and nervous system have been linked to exposure to electromagnetic fields in some studies (Tomennus, 1986; Savitz et al., 1988). Most studies have focused on low-frequency (50-60 Hz) fields, such as those associated with electric power lines and household appliances. There is very little information available concerning possible risks associated with microwave frequencies, such as from hand-held cellular telephones (800-900 MHz). While the possibility of health hazards of EMF exposure remains an active area of research, expert panels that have reviewed the existing evidence have judged that available data are insufficient to support the conclusion that EMF causes cancer (NRPB, 1992).

There is strong evidence that high doses of ionizing radiation, such as from radiotherapy, can cause tumors of the nervous system (Ron et al., 1988). The picture is less clear concerning possible risks posed by low doses of radiation. Most studies of occupationally exposed groups have not found an increased risk of brain cancer (Gilbert et al., 1989; Wang et al., 1990; Kendall et al., 1992). Radiation doses associated with diagnostic X-rays are very small and probably pose minimal, if any, risk.

Brain and Other Nervous System

Occupational exposures are implicated by the observation that brain cancer occurs more frequently among workers in certain industries: the manufacture of synthetic rubber and polyvinyl chloride, the refining of crude oil and production of petroleum-based chemicals, the manufacture of pharmaceuticals, the nuclear fuels and weapons industry, and farm work that exposes workers to agricultural chemicals (Thomas and Waxweiler, 1986). Certain professional groups, such as anatomists, pathologists, embalmers, chemists, and professional artists, appear to have higher than expected brain cancer rates. Elevated brain cancer rates also have been noted among farmers (Musicco et al., 1988; Blair et al., 1992); precision metal workers; and workers involved in electrical and electronic equipment maintenance, repair and manufacturing (Thomas and Waxweiler, 1986; Thomas et al., 1987). Exposures in these occupations are diverse and include acrylonitrile, vinyl chloride, formaldehyde, lubricating oils, N-nitroso compounds, phenols, pesticides, polycyclic aromatic hydrocarbons, organic solvents, and electromagnetic fields. Many workers are exposed to more than one of these agents, and further, detailed study is required to identify specific causal factors.

Although no single substance has yet been directly linked with excess brain cancer risk in humans, a number of chemical compounds have been shown to cause nervous system tumors in experimental animals. Brain tumors have been induced in animals with certain aromatic hydrocarbon compounds, bis-chloromethyl ether, vinyl chloride, and acrylonitrile (Kleihues et al., 1976; Maltoni et al., 1982), as well as with N-nitroso compounds. Studies with experimental animals also suggest that susceptibility to chemical and viral neurocarcinogenesis is greatest during the in utero or early postnatal period of life (Druckrey, 1973).

Certain studies have linked elevated brain tumor risk with exposure to farm animals and pets among adults (Choi et al., 1970) and children (Gold et al., 1979), raising speculation about a possible viral etiology. Other possible etiologic factors include severe head trauma and loud noise (for acoustic neuroma) (Schoenberg, 1982).

In summary, although a small percentage of cases have been identified as having a genetic or familial component, and studies have linked nervous system cancers with exposure to high-dose ionizing radiation, relatively little is known about the causes of most tumors of the nervous system. It is to be hoped that this will soon change, as results of additional studies become available.

REFERENCES

- Annegers JF, Schoenberg BS, et al.: Epidemiologic study of primary intracranial neoplasms. *Arch Neurol* 38:217-219, 1981.
- Blair A, Zahm SH, Pearce NE, et al.: Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 18:209-15, 1992.
- Bimin GR, Kuijten RR, Buckley JD, et al.: Relationship between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. *N Engl J Med* 329:536-541, 1993.
- Bimin GR, Kuijten RR, Boesel CP, et al.: Maternal diet and risk of astrocytic glioma in children: a report from the Children's Cancer Group (United States and Canada). *Cancer Causes and Control* 5:177-187, 1994a.
- Bimin GR, Buckley JD, Boesel CP, et al.: Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomarkers Prev* 3:197-204, 1994b.
- Burch JD, Craib KJP, Choi BC K, et al.: An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst* 78:601-609, 1987.
- Choi NW, Schuman LM and Gullen WH: Epidemiology of primary central nervous system neoplasms: II. Case control study. *Am J Epidemiol* 91:167-185, 1970.
- Druckrey H: Specific carcinogenic and teratogenic effects of 'indirect' alkylating methyl and ethyl compounds, and their dependency on stages of ontogenic developments. *Xenobiotica* 3:271-303, 1973.
- Gilbert ES, Fry SA, Wiggs LD, et al.: Analyses of combined mortality data on workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. *Radiat Res* 120:19-35, 1989.
- Gold E, Gordis L, Tonascia J, et al.: Risk factors for brain tumors in children. *Am J Epidemiol* 109:309-319, 1979.
- Heshmat MY, Kovi J, Simpson C, et al.: Neoplasms of the central nervous system: Incidence and population selectivity in the Washington DC Metropolitan Area. *Cancer* 38:2135-2142, 1976.
- Howe GR, Burch JD, Chiarelli AM, et al.: An exploratory case-control study of brain tumors in children. *Cancer Res* 49:4349-4352, 1989.
- Kendall GM, Muirhead CR, Macgibbon BH, et al.: Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *Br Med J* 304:220-225, 1992.
- Kleihues P, Lantos PL and Magee PN: Chemical carcinogenesis in the nervous system. *Int Rev Exp Pathol* 15:153-232, 1976.
- Kuijten RR, Bimin GR, Nass CC, et al.: Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res* 50:2608-2612, 1990.
- Kuijten RR and Bimin GR: Risk factors for childhood brain tumors. *Cancer Epidemiol Biomarkers Prev* 2:277-288, 1993.
- Kuijten RR, Strom SS, Rorke LB, et al.: Family history of cancer and seizures in young children with brain tumors: a report from the Children's Cancer Group (United States and Canada). *Cancer Causes and Control* 4:155-164, 1993.
- Magee PN: N-nitroso compounds and related carcinogens. In *Chemical Carcinogens*, ACS Monograph 173 (C.E. Searle, ed.), Washington, DC: American Chemical Society, 1976, 191-625.
- Maltoni C, Giliberti A and Carretti D: Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann NY Acad Sci* 381:216-249, 1982.
- Musico M, Silena M, Molinari S, et al.: A case-control study of brain gliomas and occupational exposure to chemical carcinogens, the risk to farmers. *Am J Epidemiol* 128:778-785, 1988.
- NRPB (National Radiologic Protection Board): Report of an advisory group on non-ionising radiation. Electromagnetic fields and the risk of cancer. Documents of the NRPB, vol 3; Chilton: NRPB, 1992.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120, World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Preston-Martin S: Descriptive epidemiology of primary tumors of the brain, cranial nerves and cranial meninges in Los Angeles County. *Neuroepidemiol* 8:283-295, 1989.

- Preston-Martin S and Henderson BE: N-nitroso compounds and human intracranial tumours. *IARC Scientific Publications* 57:887-894, 1984.
- Preston-Martin S and White SC: Brain and salivary gland tumors related to prior dental radiography: implications for current practice. *J Am Dent Assoc* 120:151-158, 1990.
- Preston-Martin S, Mack W and Henderson BE: Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res* 49:6137-6143, 1989.
- Preston-Martin S., Yu MC, Benton B, et al.: N-nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res* 42:5240-5245, 1982.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Pub. No. 94-2789, Bethesda, MD, 1994.
- Ron E, Modan B, Boice JD Jr, Alfandary E, et al.: Tumors of the brain and central nervous system after radiotherapy in childhood. *N Eng J Med* 319:1033-1039, 1988.
- Rorke LB: The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. *J Neuropathol Exp Neurol* 42:1-15, 1983.
- Sarasua S and Savitz DA: Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). *Cancer Causes Control* 5:141-148, 1994.
- Savitz DA, Wachtel H, Barnes FA, et al.: Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am J Epidemiol* 128:21-38, 1988.
- Schoenberg BS: Nervous system. In *Cancer Epidemiology and Prevention* (Schottenfeld D, Fraumeni JF Jr, eds.). Philadelphia: W. B. Saunders, in press.
- Schoenberg BS, Christine BW and Whisnant JP: The descriptive epidemiology of primary intracranial neoplasms: the Connecticut experience. *Am J Epidemiol* 104:499-510, 1976.
- Schoenberg BS, Christine BW and Whisnant JP: The resolution of discrepancies in the reported incidence of primary brain tumors. *Neurol* 28:817-823, 1978.
- Thomas TL, Stolley PD, Stemhagen A, et al.: Brain tumor mortality risk among men with electrical and electronics jobs: a case-control study. *J Natl Cancer Inst* 79:233-238, 1987.
- Thomas TL and Waxweiler RJ: Brain tumors and occupational risk factors: a review. *Scand J Work Environ Health* 12:1-15, 1986.
- Tomenius L: 50-Hz electromagnetic environment and the incidence of tumors in Stockholm County. *Bioelectromagnetics* 7:191-207, 1986.
- Wang JX, Inskip PD, Boice JD Jr, et al.: Cancer incidence among medical diagnostic x-ray workers in China, 1950 to 1985. *Int J Cancer* 45:889-895, 1990.

Breast

Celia Byrne, Ph.D.*

Breast cancer is the most common form of cancer (other than skin) and a leading cause of cancer mortality among women in the United States. Breast cancer rates in the United States are among the highest in the world. White women in the San Francisco Bay area experienced the highest incidence among 162 areas reporting incidence data to the IARC, with an annual rate of 104.2 per 100,000, adjusted to the world standard population (Parkin et al., 1992).

Incidence rates increase dramatically with age. While the rate of increase in breast cancer incidence is greatest in women under age 50, the majority of cases occur after age 50. Incidence rates in women before the age of 45 are higher among blacks; after the age of 45, they are higher for whites. Women of higher socioeconomic status, married women, women living in urban versus rural areas, and women in northern states have the highest rates.

From 1973 to 1991, invasive breast cancer incidence in the United States increased 25.8 percent in whites and 30.3 percent in blacks, or roughly 2 percent per year (Ries et al., 1994). The reason for the increase in breast cancer incidence is not clearly understood, but may be explained, in part, by a 75 percent rise in use of mammography (MMWR, 1990), since much of the increase in invasive breast cancer has been for the lowest-stage tumors. However, the increased rates cannot be completely explained by increased use of mammography, suggesting that changes in other breast cancer risk factors may also be occurring. Based on the 1983-90 statistics, the five-year relative survival rates of breast cancer were 81.6 percent for white women and 65.8 percent for black women in the United States (Ries et al., 1994). The racial disparity in survival persisted for each stage of disease.

Both genetic and environmental factors are believed to play a role in a woman's risk of developing breast cancer. If either a woman's mother or sister has breast cancer, the woman's risk increases about two to three times. Having both a mother and a sister with breast cancer increases a woman's risk up to six-fold. If that relative had bilateral breast cancer or was diagnosed at an early age, the risk may be further increased (Kelsey and Gammon, 1990). In small groups of families, the patterns of breast cancer incidence seems to be consistent with known patterns of genetic inheritance (Wright, 1990). Miki et al. reported the first cloning of a breast cancer gene (BRCA-1) in 1994. It is estimated that 86 percent of the women with a mutation in the BRCA-1 gene will develop breast cancer by age 70. However, only between 5 and 10 percent of all breast cancers seem to be attributable to an inherited genetic mutation. A second breast cancer gene (BRCA-2) has been located but not yet identified. Studies of migrants who immigrate from low-incidence areas to high-incidence areas have found that the rates of breast

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

cancer increase to that of the new country, reflecting changes in lifestyle and environmental factors, showing that international differences in rates are not due to genetic factors.

It is well recognized that certain reproductive events, and the age at which they occur, are strong determinants of subsequent breast cancer risk. The most consistent determinant of risk in various populations is the woman's age at first full-term pregnancy. Women with a first full-term pregnancy after age 30, and women who have never borne a child have about a two- to three-fold increased risk of breast cancer compared to women having a full-term pregnancy before age 20.

The greater number of women who are delaying childbirth or remaining childless may explain some of the recent increased incidence of breast cancer. Early menarche and late menopause increase a woman's risk, while removal of both ovaries, before menopause, reduces risk. Several recent studies suggest that subsequent births are associated with a further reduction in the risk of breast cancer, even after considering correlated effects of the age at first pregnancy. The effect of lactation is still not clear, although there is the suggestion of a protective effect the greater the number of months a woman breast-feeds (Kelsey et al., 1993). These reproductive factors are often thought to affect the risk of breast cancer by their effects on a woman's hormonal status.

Because of the relationship between endogenous hormones and breast cancer risk, much concern has been raised about the use of exogenous hormones. Most studies suggest no effect from oral contraceptive use on breast cancer incidence. However, some recent studies suggest a possible increase in breast cancer at an early age (before age 45) among long-term oral contraceptive users, and those who started taking oral contraceptives at a young age. There is also evidence that use of estrogen replacement therapy may slightly increase the risk of breast cancer, particularly among long-term users and those who used high doses of estrogen (Brinton and Schairer, 1993). Little is known about risk from the frequently prescribed estrogen/progestin combination. Further study of the effects of oral contraceptives and hormone replacement therapy is needed, as any associated increases in risk could affect many women.

A history of biopsy-confirmed benign breast disease is also recognized as a risk factor for breast cancer. However, the risk is not uniform for all types of benign breast disease. Atypical hyperplasia apparently indicates an especially high risk (Bodian, 1993). Women with a high degree of dense breast tissue (Dy and P2 patterns), visible on mammography, have a three to four times increased risk of breast cancer

Breast

(Oza and Boyd, 1993). A diagnosis of breast, ovarian, or endometrial cancer has also been shown to be associated with an increased risk of subsequent breast cancer.

Among postmenopausal women, breast cancer risk increases with weight and body mass. Two recent studies suggest that not only is body mass positively associated with postmenopausal breast cancer, but the distribution of weight may also be a factor (Kelsey and Gammon, 1990). Lean women appear to be at increased risk of premenopausal onset breast cancer, perhaps in part reflecting difficulties of disease detection at early ages in obese women.

Disparate levels of dietary fat consumption have been a major focus in attempting to explain some of the international and geographical differences in breast cancer incidence (the high rates in Western industrialized nations and the low rates in Asia, Latin America, and Africa). However, the results of epidemiologic studies reported to date do not resolve this issue. A few studies reported a weak increase in breast cancer risk among women consuming high fat diets, while several large prospective studies that evaluated effects of adult dietary fat intake show little if any association with breast cancer risk (Hunter and Willett, 1993).

Recent studies have shown a fairly consistent though small effect of alcohol consumption on breast cancer risk. In a summary analysis of epidemiologic studies, breast cancer risk increased between 10 and 70 percent with about two drinks daily (Longnecker et al., 1988).

Exposure to high doses of radiation, from puberty through the childbearing years—when breast tissue undergoes rapid proliferation—is known to increase the risk of breast cancer. Recent findings indicate that exposure to high doses of radiation, even in infancy, increases the risk of breast cancer in later life. The effects of low-dose radiation from mammography are considered minimal. Studies have shown that the benefits from mammography in reducing the rate of breast cancer deaths for women over 50 outweigh any possible risks (Kelsey and Gammon, 1990). However, further research is needed on the risks/benefits of mammography for women under the age of 50.

While many factors have been associated with the risk of breast cancer, most of the “established” risk factors for breast cancer are associated with only a moderate two to three times increased risk, suggesting that multiple factors may play a role in each woman’s disease and that unrecognized factors may exist. In addition, only a small proportion of the cases are accounted for by known risk factors (Kelsey and Gammon, 1990), indicating the need for further research.

REFERENCES

- Bodian CA: Benign breast diseases, carcinoma in situ, and breast cancer risk. *Epidemiol Rev* 15:177-187, 1993.
- Boring CC, Squires TS and Tong T: Cancer statistics 1994. *CA Cancer Clinic* 44:7-26, 1994.
- Brinton LA and Schairer C: Estrogen replacement therapy and breast cancer risk. *Epidemiol Rev* 15:66-79, 1993.
- Hunter DJ and Willett WC: Diet, body size, and breast cancer. *Epidemiol Rev* 15:110-132, 1993.
- Kelsey JL and Gammon MD: Epidemiology of breast cancer. *Epidemiol Rev* 12:228-240, 1990.
- Kelsey JL, Gammon MD and John EM: Reproductive and hormonal risk factors: reproductive factors and breast cancer. *Epidemiol Rev* 15:36-47, 1993.
- Longnecker MP, Berlin JA, Orza MJ, et al.: A meta-analysis of alcohol consumption in relation to risk of breast cancer. *JAMA* 260:652-656, 1988.
- MMWR (Morbidity and Mortality Weekly Report): Use of mammography—United States, 1990. *MMWR* 39:621-630, 1990.
- Oza AM, Boyd NF: Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiol Rev* 15:196-208, 1993.
- Parkin DM, Muir CS, Whelan S, et al., eds.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Pub. No. 94-2789, Bethesda, MD, 1994.
- Wright K: Breast cancer: two steps closer to understanding. *Science* 250:1659, 1990.

Childhood

Robert W. Miller, M.D.*

Though low compared with the incidence of some adult cancers, cancer is second only to accidents as the leading cause of death among children. Recent incidence rates (1990–91) of cancer among children under age 15 in this country were 14.4 per 100,000 among whites and 11.8 among blacks (Ries et al., 1994). More than 40 percent of all childhood cancers occur in the very young—age four and under (Robison LL, 1993).

More encouraging is the fact that five-year relative survival rates for many of the childhood cancers increased dramatically in this country from the 1960s to the 1970s (Ries et al., 1990; Miller and McKay, 1984). For example, the five-year survival rate for acute lymphocytic leukemia in children increased from 1 percent to almost 75 percent.

Incidence of childhood cancer varies greatly throughout the world, depending on the type. Acute lymphocytic leukemia accounts for about 78 percent of all childhood leukemia in this country, whereas acute myelomonocytic leukemia (AMML) accounts for only 4 percent. In Ankara, Turkey, almost half of all childhood leukemias are AMML. In tropical Africa, leukemia is rare, but Burkitt's lymphoma, a cancer of the lymph system, accounts for more than half of childhood cancers.

There are also varying age trends for the childhood leukemias. Among U.S. whites, Western Europeans, and, more recently, Japanese, there is a peak in leukemia incidence at about age four (Miller, 1989a). Among black children in the United States, there is little, if any, peak.

The major childhood cancers in this country are the following:

Acute Leukemias

Acute leukemias are the most frequent, with acute lymphocytic leukemia (ALL) accounting for most. The incidence is higher among boys than among girls. About 90 percent of acute lymphocytic and more than 80 percent of acute nonlymphocytic leukemia cases in children have been linked with chromosome disorders (Poplack, 1993; Grier and Weinstein, 1993).

Ionizing radiation—energetic rays that cause molecules to gain or lose electrons—can cause leukemia. When warnings about radiation were widely publicized to the medical community in the mid-1950s, safety procedures for diagnostic X-rays were tightened, use became more conservative, and, by the 1960s, leukemia incidence had fallen among all groups under age 75 (Fraumeni and Miller, 1967).

Some anticancer drugs and at least one industrial solvent, benzene, can cause leukemia in adults, but drugs, other than cancer chemotherapy, have rarely been implicated in childhood leukemia, and chemical pollutants not at all (Miller, 1989).

* From the Clinical Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Central Nervous System

Cancers of the central nervous system (the brain and spinal cord), the second most frequent cancer of childhood, account for about a fifth of cancers in children under age 15, and tend to occur in the first ten years of life. A number of genetic disorders are linked with excess risk for developing these cancers, including neurofibromatosis (Hope and Mulvihill, 1981) and the Li-Fraumeni family cancer syndrome (Li et al., 1988). Radiotherapy for ringworm of the scalp in more than 10,000 Israeli children was followed by an excess of brain cancer, with a relative risk of 6.9 when compared with the controls (Ron et al., 1988).

Lymphomas

Cancers of the lymph system are the third most common childhood cancer. Hodgkin's disease, which accounts for about half of all lymphomas, is rare in early childhood, peaking in frequency at age 25-29 and then, again, late in life. The one known exception is among the Japanese, who do not exhibit the early peak first described by MacMahon in 1966.

The non-Hodgkin's lymphomas (NHL) are also more common among boys and occasionally cluster in families as do Hodgkin's disease cases. They are linked with several rare, genetically determined, immune system diseases. Further evidence for the link of NHL with immune system disorders comes from the observations that persons who receive kidney transplants, and have thus been deliberately immunosuppressed, have a 150-fold increased risk of NHL (Hoover, 1977). Among persons with AIDS, the increased risk of NHL is close to 200-fold (Coté, 1995).

Burkitt's lymphoma, a form of non-Hodgkin's lymphoma common among African children, has been linked to malaria and Epstein-Barr virus (EBV) through the detection of raised levels of EBV antibodies (de Thé, 1985). The same unusual cell type accounts for one-third of NHL in U.S. children, but apparently has different cellular origins or pathogenesis from the disease in Africa (Magrath, 1989). Evidence of EBV infection is uncommon.

Bone Cancers

These account for about 5 percent of childhood cancers. The incidence of osteosarcoma, the most common bone cancer, peaks in late adolescence—perhaps related to a period of rapid bone growth (Miller, 1981). It usually develops in the weight-bearing bones of the legs and pelvis, particularly in the bone areas where the most growth takes place. While osteosarcoma tends to develop in some genetically caused bone lesions, Ewing's sarcoma does not. Ewing's sarcoma accounts for

Childhood

about 45 percent of bone cancers in U.S. white children, but is rare in non-white children. Because Ewing's sarcoma is seen so rarely among non-white children, there is no doubt that genetics plays a part in its development in whites.

Soft Tissue Sarcomas

Of the soft tissue sarcomas, rhabdomyosarcoma is the most common. These cancers show two distinct age peaks—one before age five, the other in the teens (Li and Fraumeni, 1969a). Rhabdomyosarcomas of the head, neck, and genitourinary system form the first peak, and there is some suspicion that these cancers form before birth.

There are several genetic disorders that predispose to sarcomas, some of which also occur as components of family cancer syndromes (Li et al., 1988).

Retinoblastoma

Retinoblastoma constitutes only 2.5 percent of childhood cancers, and about 90 percent of these children survive. Forty percent of retinoblastomas are hereditary, predominantly bilateral, and occur earlier than the nonfamilial variety, with the peak incidence occurring shortly after birth (Knudson, 1989).

In the 1960s, a few cases were found with a partial deletion of the long arm of chromosome 13, thus localizing the gene for the neoplasm. Because it shares the same gene locus, osteosarcoma occurs excessively as a double primary with retinoblastoma. The gene has recently been cloned and, through the use of DNA probes, children with a high probability of developing retinoblastoma can be identified and screened for early detection, which usually leads to a cure through surgery. When the genes from both chromosomes 13 are deleted or inactivated, they can no longer control normal growth of the retina, and neoplasia develops. Such genes, which suppress a cancer, are called tumor-suppressor genes (Knudson, 1989). Studies of this rare cancer have unlocked the mechanism of a number of common cancers, including breast, colon, and certain forms of lung cancer. High rates for this cancer have been reported in India, Pakistan, Latin American countries, and, to a lesser extent, Israel (Parkin et al., 1988).

Wilms' Tumor

Wilms' tumor, which accounts for 6 percent of childhood cancer, is a renal neoplasm with a peak incidence under five years of age. There are multiple gene loci for this cancer. An association with a rare birth defect, congenital absence of the iris of the eye, led to microscopic visualization of a partial deletion of the short arm of chromosome 11. This deletion helped locate a tumor-suppressor gene for both Wilms' tumor and the eye defect. A second gene for Wilms' tumor, associated with an overgrowth (Beckwith-Wiedemann) syndrome is at a separate locus on chromosome 11, and a third, in a family with a large aggregation of the neoplasm, is at an as yet unidentified locus, not on chromosome 11 (Coppes, 1994). Wilm's tumor has a five-year relative survival rate of 89 percent (Ries et al., 1994) and shows little variation in frequency worldwide, except among the Japanese and other Asians, who have half the usual rate (Parkin et al., 1988), as if they have a less mutable Wilms' tumor gene.

Neuroblastoma

Neuroblastoma accounts for 8 percent of childhood cancer. It is a tumor of the peripheral nervous system which arises during intrauterine life and usually becomes clinically manifest in infancy (Miller et al., 1968). There is evidence that microscopic nests of neuroblastoma cells present in the adrenal glands in late fetal life normally disappear with maturation of the fetus, and are gone by the third month of life. Rarely, when they persist, they develop into clinically detectable tumors with a five-year survival rate of 55 percent (Miller et al., 1992). The tumor-suppressor gene for this neoplasm has been localized to chromosome 1.

Neuroblastoma is virtually absent in much of East Africa, perhaps because of a maternal influence, beginning in utero, that causes regression of the microscopic nests of neuroblastoma cells, as described above (Miller, 1990).

From these rare cancers of childhood it was possible to recognize a previously unknown class of cancer genes that are involved in a broad array of cancer in people of all ages. New methods for screening, diagnosis, prevention, and treatment may now be devised.

REFERENCES

- Coppes MJ, Haber DA and Grundy PE: Genetic events in the development of Wilms' tumor. *N Engl J Med* 331(9):586-90, 1994.
- Fraumeni JF Jr and Miller RW: Leukemia mortality: Downturn in rates in the United States. *Science* 155:1126-1128, 1967.
- Grier HE and Weinstein IJ: Acute nonlymphocytic leukemia. In Principles and Practice of Pediatric Oncology, 2nd ed. (Pizzo PA, Poplack DG, eds.). Philadelphia: Lippincott, 1993.
- Hoover R: Effects of drugs—immunosuppression. In Origins of Human Cancer: Book A. Incidence of Cancer (Hiatt HH, Watson JD, Winsten JA, eds.). Cold Spring Harbor Lab. Press, New York, 1977.
- Hope DG and Mulvihill JJ: Malignancy in neurofibromatosis. *Adv Neurol* 29:33-56, 1981.
- Knudson AG Jr: Hereditary cancers disclose a class of cancer genes. *Cancer* 63:1888-1891, 1989.
- Li FP, Fraumeni JF Jr: Soft tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? *Ann Intern Med* 71:747-752, 1969.
- Li FP, Fraumeni JF Jr, Mulvihill JJ, et al.: A cancer family syndrome in twenty-four kindreds. *Cancer Res* 48:5358-5362, 1988.
- MacMahon B: Epidemiology of Hodgkin's disease. *Cancer Res* 26:1189-1200, 1966.
- Magrath TE: Non-Hodgkin's lymphomas. In Principles and Practice of Pediatric Oncology (Pizzo PA, Poplack DG, eds.). Philadelphia: Lippincott, 1989, 415-455.
- Miller RW, Fraumeni JF Jr, et al.: Neuroblastoma: Epidemiologic approach to its origin. *Am J Dis Child* 115:253-261, 1968.
- Miller RW: Contrasting epidemiology of childhood osteosarcoma, Ewing's tumor, and rhabdomyosarcoma. *J Natl Cancer Inst Monogr* 56:9-14, 1981.
- Miller RW: Frequency and environmental epidemiology of childhood cancer. pp. 3-18. In Principles and Practice of Pediatric Oncology, 2nd ed. (Pizzo PA, Poplack DG, eds.). Philadelphia: Lippincott, 1989a.
- Miller RW: No neuroblastoma in Zaire. *Lancet* 2:978-979, 1989b.
- Miller RW and McKay FW: Decline in U.S. childhood cancer mortality, 1950-1980. *JAMA* 251:1567-1570, 1984.
- Parkin DM, Stiller CA, Draper GJ, et al.: The international incidence of childhood cancer. *Int J Cancer* 42:511-520, 1988.
- Poplack DG: Acute lymphoblastic leukemia. In Principles and Practice of Pediatric Oncology, 2nd ed. (Pizzo PA, Poplack DG, eds.). Philadelphia: Lippincott, 1989.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute, NHI Pub. No. 94-2789, Bethesda, MD 1994.
- Robison LL: General principles of epidemiology in childhood cancer. pp. 3-10. In Principles and Practice of Pediatric Oncology (Pizzo PA, Poplack DG, eds.). Philadelphia: Lippincott, 1993.
- Ron E, Modan B and Boice JD Jr: Mortality after radiotherapy for ringworm of the scalp. *Am J Epidemiol* 127:713-725, 1988.
- de-Thé G: Epstein-Barr virus and Burkitt's lymphoma worldwide: The causal relationship revisited. In Burkitt's Lymphoma: A Human Cancer Model (Lenoir GM, O'Connor GT, Olweny CLM, eds.). IARC Sci. Publ. No. 60, Lyon, 1985.

Together, the colon and rectum make up the large bowel, or large intestine. The colon refers to the upper five or six feet of the large intestine, the rectum to the last five or six inches. Because of the anatomic and physiologic similarity of tissue in the colon and rectum and the occasional difficulty in determining in which region a tumor has arisen, malignancies in these two bowel segments are often lumped together as "colorectal cancer."

Colon and Rectum

Arthur G. Schatzkin,
M.D., Dr. P.H.*

Fifty-six thousand colorectal cancer deaths are estimated to have occurred in the United States in 1994 (Boring et al., 1994). It is the second leading cause of cancer death in the U.S. population as a whole, second among men and third in women. Approximately 149,000 new cases of colorectal cancer were projected for 1994, representing nearly 15 percent of all cancers diagnosed that year in this country. Colorectal cancer ranks second in cancer incidence for the combined U.S. population. Among men this is the third most commonly occurring malignancy (after prostate and lung cancers); among women it ranks third (after cancers of the breast and lung).

Five-year survival from this malignancy has improved somewhat over the past 20 years, and for patients diagnosed during 1983 through 1990, was 58 percent (Ries et al., 1994).

The incidence of colorectal cancer, as with many malignancies, is extremely low in childhood, increasing dramatically with age. SEER data for 1987–91 show, for example, that the incidence of the disease in persons 75–79 was 391/100,000; for those aged 50–54, the rate was only 51/100,000 (Ries et al., 1994). The median age at diagnosis of colorectal cancer in the United States is 70 for men and 73 for women. (Comparable median ages at diagnosis for other cancers are 63 for breast in women and 67 for lung in men.) The overall incidence of colorectal cancer is higher in men (58.9/100,000 in 1987–91) than in women (40.4/100,000), and this holds for all age groups.

Total incidence rates are comparable for whites (47.8/100,000) and blacks (52.4/100,000) (Ries et al., 1994). Rates are similar for white (58.7/100,000) and black (60.9/100,000) men, but slightly lower for white (39.9/100,000) compared to black (46.7/100,000) women. Incidence rates among blacks have caught up with those in whites over the last 15 years. Mortality rates are slightly higher in blacks than whites for both men and women.

In general, colorectal cancer rates, unlike those for cancers of the lung, cervix, and prostate, for example, show little socioeconomic gradient in the United States and other developed countries. In the United Kingdom, the elevated large intestinal cancer mortality in Social Class I (upper class) that was present at the turn of the

* From the Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

Colon and Rectum

century had essentially disappeared by 1970 (Logan, 1982). In contrast, data from Cali, Colombia (Haenszel et al., 1975), with an overall colorectal malignancy incidence much lower than that in developed countries, show a substantial excess of large bowel cancer in the upper socioeconomic strata, whose members tended to have lifestyle, including dietary, characteristics typical of more industrialized nations.

Colorectal cancer incidence and mortality vary at least ten-fold between countries with the highest and those with the lowest rates (Kurihara et al., 1984; Whelan et al., 1990). The highest incidence and mortality rates are seen in the more industrialized countries of North America, Northern and Western Europe, and New Zealand; the lowest rates are in Asia and Africa.

A rapid rise in colorectal cancer rates in a particular area signals the action of environmental factors. Such a rapid increase has been observed in Japan, where from 1969 to 1981 colorectal cancer mortality increased 14 percent in men and 40 percent in women (Kazuo et al., 1985). In the United States, from 1973 to 1991, the incidence of colorectal cancer increased 12.3 percent among men but decreased by 2.0 percent in women (Ries et al., 1994).

Numerous studies in migrants show a general convergence in colorectal cancer rates from the country of origin to the country of destination (Ziegler et al., 1985). For example, in a recent study from Australia, large bowel cancer mortality increased for persons coming from certain countries like Greece and Yugoslavia (McMichael and Giles, 1988) where rates had previously been lower. Especially noteworthy in these Australian findings is the relatively rapid convergence in colorectal cancer rates within the life span of the migrants.

In line with the evidence cited above, dietary intake varies considerably across countries, has changed over time in countries like Japan, and may be altered substantially during acculturation following migration. Moreover, food (or its various metabolites) affects several potentially important intestinal processes and comes into direct contact with gastrointestinal epithelial tissue (Bruce, 1987).

Animal experiments have shown dietary fat to promote large bowel tumors (Reddy, 1983). The international correlation between per capita fat consumption and colorectal cancer rates is very strong (Draser, 1973). Epidemiologic studies have generally shown a direct association between fat intake and colorectal cancer risk. In a prospective cohort study of approximately 90,000 nurses, investigators found that women in the highest of five categories of daily animal fat intake, compared to those in the lowest category, had nearly twice the risk of developing colon cancer (Willett et al., 1990). Evidence indicates that most colorectal cancers originate as

Colon and Rectum

benign growths of the intestinal lining, called adenomatous polyps. In a recently reported investigation of male health professionals with adenomatous polyps, men in the highest category of dietary fat intake had twice the risk of adenomatous polyps as those in the lowest quintile (Giovannucci et al., 1990).

A number of studies have found an association between red meat consumption and colorectal cancer. The prospective study of nurses, for example, found that women with the highest ratio of red meat to chicken and fish intake had two and one-half times the colon cancer risk of those with the lowest ratio (Willett et al., 1990). A prospective cohort study of nearly 50,000 U.S. male health professionals showed that men who ate beef, pork, or lamb as a main dish, compared to those consuming these foods less than once a month, had over three times the risk of colon cancer (Giovannucci et al., 1994). Cooked meats have been found to contain compounds, including a class of heterocyclic amines, which are mutagenic and carcinogenic in animal models. They are produced during high-temperature cooking such as broiling or frying (Sugimura, 1986).

Countries and regions with the highest per capita dietary fiber consumption tend to have the lowest colorectal cancer rates. A recent meta-analysis of 16 case-control studies found nearly a 35 percent reduction in the relative risk of colorectal cancer for those in the highest, compared to the lowest, category of dietary fiber intake (Trock, 1990). In the cohort study of polyps in male health professionals, men in the highest, relative to those in the lowest, category of dietary fiber intake had half the risk of developing an adenomatous polyp of the large bowel (Giovannucci et al., 1990).

The large majority of case-control studies of colorectal cancer that assessed vegetable intake found it to be protective (Potter, 1993). Several case-control studies of large bowel cancer have shown an inverse association for fruit intake, but in general the analytic epidemiologic findings are not as consistent for fruits as for vegetables (Slattery et al., 1988). Because vegetables are a major source of dietary fiber in industrialized countries, the observed protective association for vegetables might be due to fiber or the joint effect of fiber and specific anticarcinogens found in vegetables. Recent investigations have suggested that intake of folic acid, found in many vegetables, may reduce the risk of colorectal cancer (Glynn and Albanes, 1994).

One international correlation study has shown generally higher calcium consumption in countries with lower colorectal cancer rates, but the number of data points was rather small (Sorenson et al., 1988a). Garland and his colleagues spurred epidemiologic interest in this question with their report from the prospective Western Electric Study of an inverse calcium-large bowel cancer association (Garland et al.,

Colon and Rectum

1985), a finding confirmed in some but not all subsequent studies (Sorenson et al., 1988b). Some recent studies have observed that intake of vitamin D reduces colorectal cancer risk (Bostick et al., 1993).

Several epidemiologic investigations have shown a direct association between alcohol ingestion and colorectal cancer, particularly for beer and rectal cancer, whereas other studies have found minimal or no association. A recent meta-analysis of 27 studies concluded that the increased risk of colorectal cancer in relation to alcoholic beverage consumption was at best small and not clearly indicative of a causal role (Longnecker et al., 1990).

Colorectal cancer mortality in the United States has tended to be concentrated in regions of past intense industrial activity (North Atlantic Coast, New Jersey, Massachusetts, New York, and the urban Great Lakes area) (Spiegelman and Wegman, 1985). In a number of occupational cohort studies, colon cancer rates have been moderately increased (Lashner and Epstein, 1990). Data on potential occupational colorectal carcinogens, however, tend to be sparse and at the present time there is insufficient evidence to conclude that a substantial proportion of colorectal cancer incidence in the United States results from workplace exposure.

A number of epidemiologic studies have now found that regular use of aspirin is associated with a reduced risk of colorectal cancer, although the evidence on this link is not wholly consistent (Garewal, 1994). Some epidemiologic and clinical studies have suggested that other nonsteroidal anti-inflammatory drugs (NSAID) may protect against colonic neoplasia. NSAID affect prostaglandin synthesis in humans and have been shown to inhibit chemically induced colorectal tumor formation in animal models (Pollard and Luckert, 1980; Metzger et al., 1984). The possible protective effect of aspirin and other NSAID on colorectal carcinogenesis is an active area of research.

Other epidemiologic studies have found a small direct association between obesity and risk of large bowel malignancy (Wu et al., 1987). Because cancer itself may cause weight loss, it is important to ascertain weight some years prior to diagnosis.

Case-control studies have found little association between height and large bowel cancer, but a direct association was observed in two cohort studies (Chute et al., 1991; Albanes et al., 1988). These cohorts, however, could not be said to reflect much range of nutritional deprivation, and therefore a nutritional explanation for these height-colorectal cancer findings is tenuous.

Colon and Rectum

An association between low physical activity and large bowel malignancy has become one of the most consistent epidemiologic findings for this disease in recent years. Well over a dozen studies, both case-control and cohort, employing several different methods of physical activity assessment, have demonstrated this association (Lee et al, 1991). The association with colorectal cancer has been noted for both occupational and leisure-time activity.

The extent to which genetic factors, in isolation or in interaction with environmental factors, play a role in sporadic cancers is unresolved. Family history of colorectal cancer in a first-degree relative has been estimated to confer approximately a three-fold risk of this malignancy. Analyses of kindreds in Utah have been interpreted to indicate a dominant pattern of inheritance for susceptibility to adenomatous polyps and colorectal cancer (Cannon-Albright et al., 1988). Investigators have recently identified mutated genes involved in the development of familial adenomatous polyposis (FAP) (Grodén et al., 1991), a rare inherited condition that is characterized by many hundreds of large intestinal polyps and progresses to cancer with a very high frequency, and hereditary nonpolyposis colon cancer (HNPCC) (Leach et al., 1993), a familial syndrome in which affected individuals develop tumors of the colon (and other organs) often before 50 years of age. Scientists are continuing to explore genetic defects that may be involved in the development and progression of colorectal cancer.

Large bowel cancer mortality rates have declined for white men and women in the United States in recent years. Investigators have recently presented evidence linking this decline to improved early detection procedures (Chu et al., 1994). The increased use of sigmoidoscopy and fecal occult blood tests (followed by colonoscopy) may have played an important role in reducing mortality from large bowel cancer.

REFERENCES

- Albanes D, Jones DY, Schatzkin A, et al.: Adult stature and risk of cancer. *Cancer Res* 48:1658-62, 1988.
- Anderson DE: Risk in families of patients with colon cancer. pp. 109-115. In *Colorectal Cancer: Prevention, Epidemiology and Screening*. (Schottenfeld D, Sherlock P, Winawar SJ, eds.). New York: Raven Press, 1980.
- Boring CC, Squires TS, Tong T: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Bostick RM, Potter JD, Sellers TA, et al.: Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women: The Iowa Women's Health Study. *Am J Epidemiol* 137:1302-17, 1993.
- Bruce WR: Recent hypotheses for the origin of colon cancer. *Cancer Res* 47:4237-42, 1987.
- Cannon-Albright LA, Skolnick MH, Bishop DT, et al.: Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. *N Engl J Med* 319:533-7, 1988.
- Chu KC, Tarone RE, Chow WH, et al.: Temporal patterns in colorectal cancer incidence, survival, and mortality from 1950 through 1990. *J Natl Cancer Inst* 86:997-1006, 1994.
- Clute CG, Willett WC, Colditz GA, et al.: A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women. *Cancer Causes Control* 2:117-21, 1991.
- Drasar BS and Irving D: Environmental factors and cancer of the colon and breast. *Br J Cancer* 27:167-72, 1973.
- Garewal H: Aspirin in the prevention of colorectal cancer. *Ann Intern Med* 121:303-4, 1994.
- Garland C, Shekelle RB, Barrett-Connor E, et al.: Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* 1:307-9, 1985.
- Giovannucci E, Rimm EB, Stampfer MJ, et al.: Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390-7, 1994.
- Giovannucci E, Stampfer MJ, Colditz GA, et al.: Relation of diet to risk of colorectal adenoma in men. *Am J Epidemiol* 132:783, 1990.
- Glynn SA and Albanes D: Folate and cancer: A review of the literature. *Nutr and Cancer* 22:101-19, 1994.
- Groden J, Thliveris A, Samowitz W, et al.: Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 66:589-600, 1991.
- Haenszel W, Correa P and Cuello C: Social class differences among persons with large-bowel cancer in Cali, Colombia. *J Natl Cancer Inst* 54:1031-5, 1975.
- Kazuo I, Hirose K, Nakagawa N, et al.: Urban-rural difference in the trend of colo-rectal cancer mortality with special reference to the subsites of colon cancer in Japan. *Jpn J Cancer Res (Gann)* 76:717-28, 1985.
- Kurihara M, Aoki K and Tomimaga S: Cancer mortality statistics in the world. Nagoya, Japan: University of Nagoya Press, 1984.
- Lashner BA and Epstein SS: Industrial risk factors for colorectal cancer. *Int J Health Serv* 20:459-83, 1990.
- Leach FS, Nicolaides NC, Papadopoulos N, et al.: Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. *Cell* 75:1215-25, 1993.
- Lee IM, Paffenbarger RS and Hsieh CC: Physical activity and risk of developing colorectal cancer among college alumni. *J Natl Cancer Inst* 83:1324-9, 1991.
- Logan WPD: Cancer mortality by occupation and social class 1851-1971. London: Her Majesty's Stationery Office. Studies on Medical and Population Subjects No. 44, 1982.
- Longnecker MP, Orza MJ, Adams ME, et al.: A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. *Cancer Causes Control* 1:59-68, 1990.
- McMichael AJ and Giles GG: Cancer in migrants to Australia: Extending the descriptive epidemiological data. *Cancer Res* 48:751-6, 1988.
- Metzger U, Meier J, Uhlenschmid G, et al.: Influence of various prostaglandin synthesis inhibitors on DMH-induced rat colon cancer. *Dis Colon Rectum* 27:366-9, 1984.
- Pollard M and Luckert PH: Indomethacin treatment of rats with dimethylhydrazine-induced intestinal tumors. *Cancer Treat Rep* 64:1323-7, 1980.
- Potter JD, Slattery ML, Bostick RM, et al.: Colon cancer: A review of the epidemiology. *Epidem Rev* 15:499-545, 1993.
- Reddy BS: Dietary fat and colon cancer. Experimental Colon Carcinogenesis. pp. 225-239. (Astrup H, Williams GM, eds.). Boca Raton, Florida, CRC Press, Inc., 1983.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs. National Cancer Institute, NIH Pub. No. 94-2789, Bethesda, MD 1994.

- Slattery ML, Sorenson AW, Mahoney AW, et al.: Diet and colon cancer: Assessment of risk by fiber type and food source. *J Natl Cancer Inst* 80:1474-1480, 1988.
- Sorenson AW, Slattery ML and Ford MH: Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* 128(3):504-514, 1988a.
- Sorenson AW, Slattery ML and Ford MH: Calcium and colon cancer: A review. *Nutr Cancer* 11:135-45, 1988b.
- Spiegelman D, Wegman DH: Occupation-related risks for colorectal cancer. *J Natl Cancer Inst* 75:813-21, 1985.
- Sugimura T: Past, present, and future of mutagens in cooked foods. *Environ Health Perspect* 67:5-10, 1986.
- Trock B, Lanza E and Greenwald P: Dietary fiber, vegetables, and colon cancer: critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* 82:650-61, 1990.
- Whelan SL, Parkin DM and Masuyer E: Patterns of cancer in five continents. Lyon, France: International Agency for Research on Cancer. IARC Scientific Publication No. 102, 1990.
- Willett WC, Stampfer MJ, Colditz GA et al.: Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *New Engl J Med* 323:1664-72, 1990.
- Wu AH, Paganini-Hill A, Ross RK, et al.: Alcohol, physical activity and other risk factors for colorectal cancer. A prospective study. *Brit J Cancer* 55:687-94, 1987.
- Ziegler RG, Devesa SS and Fraumeni JF: Epidemiologic patterns of colorectal cancer, pp. 209-32. In *Important Advances in Oncology*. (DeVita VT Jr, Hellman S, Rosenberg SA, eds.). Philadelphia: J.P. Lippincott, 1985.

Esophagus

Linda Morris Brown, M.P.H.*

Esophageal cancer is a malignancy that is well known for its marked variation by geographic area, ethnic group, and sex (Day and Munoz, 1982). In the United States, esophageal cancer accounts for only 1 percent of all cancers. However, this figure rises to almost 3 percent in black males (Ries et al., 1994). Annual U.S. incidence rates among blacks (17.1 per 100,000 males, 4.7 per 100,000 females) are more than three times those of whites (5.5 per 100,000 males, 1.7 per 100,000 females), and rates among males are more than three times those of females. The 5-year relative survival is poor—10 percent for whites and 6 percent for blacks (Ries et al., 1994). While the majority of esophageal cancers in the United States are squamous cell carcinomas, the incidence of adenocarcinomas appears to be rising, especially among white men (Blot et al., 1991). In 1987, adenocarcinomas accounted for 31 percent of all esophageal cancers in white men, 12 percent in white women, but only 3 percent and 1 percent, respectively, in black men and women (Blot et al., 1991). Many of the adenocarcinomas tend to arise from a medical condition known as Barrett's esophagus (Williamson et al., 1991).

International differences in esophageal cancer incidence as published in Volume VI of *Cancer Incidence in Five Continents* (Parkin et al., 1992) are striking. World standardized rates among males are highest in Calvados, France (26.5 per 100,000), and lowest in Israeli Jews (0.6 per 100,000). Rates among females range from 0.1 per 100,000 among Los Angeles Japanese to 8.8 per 100,000 in Bangalore, India. Rates for U.S. blacks rank among the highest in the world, while those for U.S. whites rank among the lowest. Internationally, the male/female rate ratio varies from less than two to more than 20.

In Western countries, 80 to 90 percent of the risk of squamous cell carcinoma of the esophagus can be attributed to consumption of alcohol and tobacco (Day and Munoz, 1982; Schottenfeld, 1984). Alcohol and tobacco appear to act independently, with the importance of each factor depending on the population under study (Tuyts, 1983). In a population of heavy drinkers, the major factor appears to be alcohol (Tuyts, 1983; Pottern et al., 1981), whereas tobacco is likely to be the most important factor in a population of heavy smokers (Wynder and Bross, 1961). Although little is known about the epidemiology of adenocarcinoma of the esophagus, the roles of tobacco and alcohol appear to be less important than for squamous cell carcinoma and do not explain the rapid rise in incidence of this tumor. Increases in the prevalence of obesity, however, may explain at least a portion of the recent increase (Brown et al., 1995; Vaughan et al., 1995).

The type of alcoholic beverage associated with the greatest risk of esophageal cancer in the majority of the American studies was hard liquor (Pottern et al., 1981; Wynder and Bross, 1961; Brown et al., 1988; Yu et al., 1988); however, in a couple of studies beer consumption was found to be the major determinant of risk (Kaul et al., 1986; Graham et al., 1990). Consumption of moonshine or other home-

* Office of the Associate Director, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

brewed alcoholic beverages has also been associated with excess risk of esophageal cancer in populations where these beverages are commonly used (Brown et al., 1988; Tuyns et al., 1979; Martinez, 1969).

In most studies, the risk of developing cancer of the esophagus was significantly increased among tobacco users, regardless of whether cigarettes, cigars, or pipes were smoked (Brown et al., 1994b; Yu et al., 1988; Tuyns and Esteve, 1983). Subjects who had quit smoking for 10 or more years appeared to have significantly reduced risks compared to current smokers (Brown et al., 1988; Yu et al., 1988).

A number of studies have shown an association between esophageal cancer and low socioeconomic status, independent of smoking and drinking, which may be associated with an inadequate diet (Day and Munoz, 1982; Schottenfeld, 1984). Poor nutrition in general has been suspected to be a cause of esophageal cancer. In Iran (Cook-Mozaffari et al., 1979), the Soviet Union (Kolicheva, 1980), and China (Yang et al., 1984), esophageal cancer is endemic in regions with limited diets and impoverished agriculture. Consumption of very hot beverages and the attendant possible thermal injury to the esophagus have also been considered a potential risk factor for esophageal cancer in less developed countries (DeJong et al., 1974; Victora et al., 1987; Ghadirian, 1987).

Data based on experimental animal diet studies (Gabrial et al., 1982), correlation studies involving areas of high and low esophageal cancer incidence (Van Rensburg, 1981) and on environmental studies conducted in high-risk areas of China (Yang et al., 1984) have suggested that decreased levels of specific nutrients (carotene, ascorbic acid, riboflavin, niacin, thiamin, zinc, magnesium, and selenium) may play a role in the etiology of esophageal cancer. Case-control studies in the United States (Brown et al., 1988; Yu et al., 1988; Graham et al., 1990; Ziegler et al., 1981), Puerto Rico (Martinez, 1969), Iran (Cook-Mozaffari et al., 1979), France (Tuyns 1983; Tuyns et al., 1987) and Italy (Decarli et al., 1987) have demonstrated an association between reduced consumption of certain basic food groups, notably fruits and vegetables, and esophageal cancer. Many of these studies have also reported a protective effect of vitamin C.

Until recently, esophageal cancer was unusually common in women from the rural, northern areas of Sweden, many of whom also had the Plummer-Vinson syndrome, which is associated with vitamin and iron deficiencies (Larsson et al., 1975). Chronic use of alcohol has been associated with deficiencies in vitamins A, C, D, the B vitamins, zinc, and protein (Broitman, 1983). Smoking may also contribute to vitamin C deficiencies (Kallner, 1981).

In the United States, use of tobacco and alcohol accounts for the majority of esophageal cancers, with nutritional factors also playing a role. Racial differences in susceptibility to the carcinogenic effects of alcohol and tobacco may explain, in part, the excess of squamous cell esophageal cancer in blacks compared to whites (Brown et al., 1994b).

REFERENCES

- Blot WJ, Devesa SS, Kneller RW, et al.: Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 265:1287-1289, 1991.
- Broitman SA, Vitale JJ and Gottlieb LS: Ethanol beverage consumption, cigarette smoking, nutritional status, and digestive tract cancers. *Semin Oncol* 10:322-329, 1983.
- Brown LM, Blot WJ, Schuman SH, et al.: Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *J Natl Cancer Inst* 80:1620-1625, 1988.
- Brown LM, Silverman DT, Pottern LM, et al.: Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: Alcohol, tobacco and socioeconomic factors. *Cancer Causes Control* 5:333-340, 1991.
- Cook-Mozaffari PJ, Azordegan F, Day NE, et al.: Oesophageal cancer studies in the Caspian Littoral of Iran: Results of a case-control study. *Br J Cancer* 39:293-309, 1979.
- Day NE and Munoz N: Esophagus. In *Cancer Epidemiology and Prevention*. (Schottenfeld D, Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders Company, 1982.
- Decarli A, Liati P, Negri E, et al.: Vitamin A and other dietary factors in the etiology of esophageal cancer. *Nutr Cancer* 10:29-37, 1987.
- DeJong UW, Breslow N, Hong J, et al.: Aetiological factors in oesophageal cancer in Singapore Chinese. *Int J Cancer* 13:291-303, 1974.
- Gabrial GM, Schrager TF and Newberne PM: Zinc deficiency, alcohol, and a retinoid: Association with esophageal cancer in rats. *J Natl Cancer Inst* 68:785-789, 1982.
- Ghadirian P: Thermal irritation and oesophageal cancer in Northern Iran. *Cancer* 60:1909-1914, 1987.
- Graham S, Marshall J, Haughey B, et al.: Nutritional epidemiology of cancer of the esophagus. *Am J Epidemiol* 131:454-467, 1990.
- Kallner AB, Hartmann D and Hornig DH: On the requirements of ascorbic acid in man: Steady-state turnover and body pool in smokers. *Am J Clin Nutr* 34:1347-1355, 1981.
- Kaul L, Nidiry JJ, Charles-Marcel Z, et al.: Diet and esophageal cancer: A case-control study. *Nutr Res* 6:905-912, 1986.
- Kolichova NE: Epidemiology of esophagus cancer in the USSR. In *Joint USA/USSR Monograph on Cancer Epidemiology in the USA and USSR*. (Levin D, ed.). Washington, DC: DHHS (DHHS Publ. No. 80-2041), 1980.
- Larsson LG, Sandstrom A and Westling P: Relationship of Plummer-Vinson disease to cancer of the upper alimentary tract in Sweden. *Cancer Res* 35:3308-3316, 1975.
- Martinez I: Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst* 42:1069-1094, 1969.
- Parkin DM, Muir CS, Whelan S, et al., eds.: *Cancer Incidence in Five Continents*, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Pottern LM, Morris LE, Blot WJ, et al.: Esophageal cancer among black men in Washington, DC. I. Alcohol, tobacco, and other risk factors. *J Natl Cancer Inst* 67:777-783, 1981.
- Ries LAG, Miller BA, Hankey BF, et al.: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*. National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Schottenfeld D: Epidemiology of cancer of the esophagus. *Semin Oncol* 11:92-100, 1984.
- Tuyns AJ: Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. *Int J Cancer* 32:443-444, 1983.
- Tuyns AJ, Pequignot G and Abbaticci JS: Oesophageal cancer and alcohol consumption: Importance of type of beverage. *Int J Cancer* 23:443-447, 1979.

- Tuyns AJ and Esteve J: Pipe, commercial and hand-rolled cigarette smoking in oesophageal cancer. *Int J Epidemiol* 12:110-113, 1983.
- Tuyns AJ: Protective effect of citrus fruit on esophageal cancer. *Nutr Cancer* 5:195-200, 1983.
- Tuyns AJ, Riboli E, Doornbos G, et al.: Diet and esophageal cancer in Calvados (France). *Nutr Cancer* 9:81-92, 1987.
- Van Rensburg SJ: Epidemiologic and dietary evidence for a specific nutritional predisposition to esophageal cancer. *J Natl Cancer Inst* 67:243-251, 1981.
- Victora CG, Munoz N, Day NE, et al.: Hot beverages and oesophageal cancer in Southern Brazil: A case-control study. *Int J Cancer* 39:710-716, 1987.
- Williamson WA, Ellis FH Jr., Gibb SP, et al.: Barrett's esophagus. Prevalence and incidence of adenocarcinoma. *Arch Intern Med* 151:2212-2216, 1991.
- Wynder EL and Bross IJ: A study of etiological factors in cancer of the esophagus. *Cancer* 14:389-413, 1961.
- Yang CS, Sun Y, Yang Q, et al.: Vitamin A and other deficiencies in Linxian, a high esophageal cancer incidence area in Northern China. *J Natl Cancer Inst* 73:1449-1453, 1984.
- Yu MC, Garabrant DH, Peters JM, et al.: Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Res* 48:3843-3848, 1988.
- Ziegler RG, Morris LE, Blot WJ, et al.: Esophageal cancer among black men in Washington, DC. II. Role of nutrition. *J Natl Cancer Inst* 67:1199-1206, 1981.

Hodgkin's Disease

Paul H. Levine, M.D.*

Hodgkin's disease is a form of cancer involving the lymphatic system. In 1994, there were an estimated 7,900 new cases (4,400 men and 3,500 women) and 1,550 deaths (900 men and 650 women) (Ries et al., 1994). From 1973 to 1991, mortality rates from Hodgkin's disease declined more than 50 percent, largely because of more effective therapy (mortality rates for 1987-91 were 0.7/100,000 men and 0.4/100,000 women). In the United States, Hodgkin's disease is relatively rare in children. However, two incidence peaks occur, between the ages of 15 and 34 and after age 45, which suggest different etiologies in these two age groups (MacMahon, 1957).

The patterns of this disease differ from one country to another. In developing countries, for example, childhood Hodgkin's disease is far more common than the adult manifestation (Correa and O'Connor, 1971), indicating the importance of environmental factors in the cause of this disease. Italy, Switzerland, Canada, and the United States experienced the highest incidence rates in the world for this relatively rare cancer (Parkin et al., 1992). The world standardized rate for U.S. white males was 3.4/100,000. The rate for U.S. black males was nearly half that for white males. For both races, rates for females were lower than those for males. In general, developed countries, particularly Scandinavian countries and the United States, have the highest incidence of Hodgkin's disease among 15- to 34-year-olds. There is a notable and unexplained exception in Japan, where only the older age group (greater than 45) is affected.

There are several histopathologic subtypes of the disease that not only hold great prognostic importance but also suggest different causality. Childhood Hodgkin's disease in developing countries is usually of the mixed cellularity or lymphocyte depletion histopathologic subtype associated with a higher frequency of Reed-Sternberg cells. This important morphologic feature of Hodgkin's disease generally correlates with poor prognosis. The nodular sclerosis form of Hodgkin's disease is seen most frequently in young women in developed countries and is usually associated with a good prognosis, though a subclass designated lymphocyte-depleted nodular sclerosis has a poorer prognosis than other nodular sclerosis cases (Axtell et al., 1972). Current information suggests that many cases of lymphocyte-predominant Hodgkin's disease are B-cell tumors and may be a different entity from other forms of Hodgkin's disease (Wright, 1989). In general, the prognosis is better in those cases with greater numbers of lymphocytes and fewer Reed-Sternberg cells. Stage of disease is another important factor determining prognosis; patients with stage I and stage II Hodgkin's disease, the more limited forms, are more likely to be cured by therapy than those with more advanced stage III and stage IV disease.

* From the Viral Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Infection

Hodgkin's Disease

In the early descriptions of Hodgkin's disease, clinicians noted the frequent appearance of fever and enlarged cervical lymph nodes, which suggested an infectious etiology for this disease. Subsequent reports noted the appearance of clusters of Hodgkin's disease (Vianna et al., 1971; Grufferman, 1982), and several studies have suggested that siblings of patients with Hodgkin's disease are at higher risk of developing this malignancy (Grufferman, 1982). There is considerable disagreement, however, as to whether these clusters are biologically meaningful or an artifact of reporting of coincidental occurrences (National Conference on Clustering of Health Events, 1990). Additional reports suggesting an infectious etiology include geographic patterns (Cole et al., 1968), noting a higher mortality rate in the Northern United States than in the South for young adult Hodgkin's disease. This pattern was not apparent for Hodgkin's disease in the older population, again indicating different etiologies for these two age groups. A number of investigators have noted parallels to other illnesses known or suspected of having an infectious etiology. Polio, for example, which affects younger people in developing countries more often than in developed countries, parallels the incidence pattern of Hodgkin's disease in developing versus developed countries. In addition, multiple sclerosis, where the risk of disease is related to place of birth, has also been noted to have a geographic pattern similar to that of Hodgkin's disease (Newell, 1970).

The two viruses that have been linked most specifically to Hodgkin's disease are Epstein-Barr virus (EBV) and the more recently discovered human herpesvirus-6 (HHV-6). Of particular interest is the association between Hodgkin's disease and infectious mononucleosis, a disease known to be caused by EBV and, rarely, other herpes viruses, including HHV-6. Several studies have shown that young adults developing infectious mononucleosis have a significantly higher risk of developing Hodgkin's disease within five years of their infectious mononucleosis (Grufferman, 1982). Whether this is a direct result of the infection with EBV or whether it is a result of the depressed immunity known to accompany infectious mononucleosis (Lantorp et al., 1972; Mangi et al., 1974) is unknown, but it is apparent that five years after the occurrence of infectious mononucleosis, the risk of developing Hodgkin's disease returns to normal.

Infection with EBV at an early age is rarely accompanied by significant clinical signs or symptoms but, as with most herpes viruses, the first infection at a later age produces a much more severe clinical illness. Therefore, infectious mononucleosis is largely a disease of individuals in upper socioeconomic groups who escape early infection; it is also of interest that, in the United States, Hodgkin's disease in the younger age groups is largely a disease of upper socioeconomic status (Gutensohn, 1982). Laboratory data first linking EBV (then called herpes-type virus) to the mixed cellularity and lymphocyte depletion forms of Hodgkin's disease was first

Hodgkin's Disease

reported in 1970 in the United States (Levine et al., 1970, 1971) and was partly confirmed in Sweden (Johanssen et al., 1970), where a different histologic classification was used. Although an etiologic role for EBV was suspected because of the relationship of antibody titers to stage of disease and to histologic subtype in patients before therapy (Levine et al., 1971), more convincing data were developed with a prospective serologic study (Mueller et al., 1989) and the detection of EBV in the Reed-Sternberg cells of biopsies taken from patients with Hodgkin's disease (Weiss et al., 1989). The relationship between EBV and Hodgkin's disease has been clarified even further by recent reports detecting EBV in the lymph node biopsies of children and older adults (but less frequently in young adults) (Jarrett et al., 1992) and the identification of EBV tumor-associated gene products in Hodgkin's disease tumor cells (Pallesen et al., 1991). Because infectious mononucleosis is known to have more than one causative agent, it is possible that Hodgkin's disease also can result from more than one infectious agent. Evidence for a role for HHV-6 was described (Clark et al., 1990; Torelli et al., 1991), but longitudinal studies suggest that the antibody titers to HHV-6 reflect a response to therapy, unlike EBV, and therefore an etiologic role is less likely (Levine et al., 1992; Levine et al., in press [b]).

Occupation

The strongest occupational link to Hodgkin's disease was first noted by Acheson, who reported an increased incidence in woodworkers (1967). Support for this finding occurred in a series of studies summarized by Grufferman (1982). Phenoxacetic herbicides have been associated with Hodgkin's disease in one study (Hardell et al., 1981), but this report is unconfirmed, and the significance of this association has been questioned (Hoar et al., 1986).

Other Factors

Genetic susceptibility does not appear to be of major importance in Hodgkin's disease (Fraumeni and Li, 1969). The evidence for a genetic predisposition to Hodgkin's disease is primarily limited to the association with ataxia telangiectasia (AT), a genetically determined abnormality of the immune system, but because other lymphomas are even more prominent in AT patients (Spector et al., 1982), the association is probably the result of the immunosuppressed state and not of a specific genetic predisposition to Hodgkin's disease. Certain genetic markers have been associated with Hodgkin's disease (Forbes and Morris, 1970), and familial occurrences, though rare, have been described (Grufferman, 1982; Chakravarti, 1986). It has been estimated that most of these cases are the result of genetic susceptibility (Chakravarti, 1986; Levine, in press [b]). Other reported associations, such as tonsillectomy and amphetamine usage, have not been confirmed as contributing to the etiology of Hodgkin's disease (Grufferman, 1982; Mueller et al., 1987).

REFERENCES

- Acheson ED: Hodgkin's disease in woodworkers. *Lancet* ii:988-989, 1967.
- Axtel LM, Myers MH, Thomas LH, et al.: Prognostic indicators in Hodgkin's disease. *Cancer* 29:1481-1488, 1972.
- Boring CC, Squires TS and Tong T: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Chakravati A, Hallorau SL, Bale SJ et al.: Etiologic heterogeneity in Hodgkin's disease: HLA linked and unlinked determinants of susceptibility independent of histological concordance. *Genet Epidemiol* 3(6):407-415, 1986.
- Clark DA, Alexander FE, McKinney PA, et al.: The epidemiology of human herpesvirus-6 (HHV-6) from a case-control study of leukaemia and lymphoma. *Int J Cancer* 45:829-833, 1990.
- Cole P, MacMahon B and Aisenberg A: Mortality from Hodgkin's disease in the U.S.: Evidence for the multiple aetiology hypothesis. *Lancet* 2(583):1371-1376, 1968.
- Correa P and O'Connor GT: Epidemiologic patterns of Hodgkin's disease. *Int J Cancer* 8:192-201, 1971.
- Forbes JF and Morris PJ: Leucocyte antigens in Hodgkin's disease. *Lancet* 2(678):849-851, 1970.
- Fraumeni JF Jr and Li FP: Hodgkin's disease in childhood: An epidemiologic study. *J Natl Cancer Inst* 42:681-691, 1969.
- Grufferman S: Hodgkin's Disease. In *Cancer Epidemiology and Prevention*. (Schottenfeld D, Fraumeni, JF Jr, eds.). Philadelphia: W. B. Saunders, 739-753, 1982.
- Gutensohn NM: Social class and age at diagnosis of Hodgkin's disease: New epidemiologic evidence for the "two-disease hypothesis." *Cancer Treat Rep* 66:689-695, 1982.
- Hardell L, Eriksson M, Lenner P, et al.: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 43:169-176, 1981.
- Hoar SK, Blair A, Holmes FF, et al.: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 256:1141-1147, 1986. [Published erratum appears in JAMA 1986 Dec.]
- Jarrett RF, Gallagher A, Jones DB, et al.: Detection of Epstein-Barr virus genomes in Hodgkin's disease: Relation to age. *J Clin Path* 44:844-848, 1991.
- Johansson B, Klein G, Henle Wet, et al.: Epstein-Barr virus (EBV)-associated antibody patterns in malignant lymphoma and leukaemia. I. Hodgkin's disease. *Int J Cancer* 6:450-462, 1970.
- Lantorp K, Wahren B and Hanngren A: Infectious mononucleosis and depression of cellular immunity. *BMJ* 4:668, 1972.
- Levine PH, Ablashi DV, Berard CW, et al.: Elevated antibody titers to herpes-type virus in Hodgkin's disease. *Proc Am Assoc Cancer Res* 11:49, 1970.
- Levine PH, Ablashi DV, Berard CW, et al.: Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. *Cancer* 27:416-421, 1971.
- Levine PH, Ebbesen P, Ablashi DV, et al.: Antibodies to human herpes virus-6 and clinical course in patients with Hodgkin's disease. *Int J Cancer* 51:53-57, 1992.
- Levine PH, Lin A and Tucker MA: What can we learn about the etiology of Hodgkin's disease from family studies? In *The Aetiology of Hodgkin's Disease*. (Jarrett R, ed.). London: Plenum Press (in press) (a).
- Levine PH, Manak M and Jagodzinski L: Hodgkin's disease and human herpesvirus-6: A model for studies of new etiologic agents. In *The Aetiology of Hodgkin's Disease*. (Jarrett R, ed.). London: Plenum Press, (in press) (b).
- MacMahon B: Epidemiologic evidence on the nature of Hodgkin's disease. *Cancer* 10:1045-1054, 1957.
- Mangi RJ, Niederman JC and Helleher JE Jr: Depression of cell-mediated immunity during acute infectious mononucleosis. *N Engl J Med* 291:1149-1153, 1974.
- Mueller N: An epidemiologist's view of the new molecular biology findings in Hodgkin's disease. *Ann Oncol* (suppl) 2:23-28, 1991.
- Mueller N, Evans A, Harris NL, et al.: Hodgkin's disease and Epstein-Barr virus: Altered antibody pattern before diagnosis. *N Engl J Med* 320:689-695, 1989.
- Mueller N, Swanson GM, Hsieh CC, et al.: Tonsillectomy and Hodgkin's disease: Results from companion population-based studies. *J Natl Cancer Inst* 78:1-5, 1987.

- National Conference on Clustering of Health Events:
Am J Epidemiol (suppl) 132:S1-S202, 1990.
- Newell GR: Etiology of multiple sclerosis and Hodgkin's disease. *Am J Epidemiol* 2:119-122, 1970.
- Pallesen G, Hamilton-Dutoit SJ, Rowe M, et al.: Expression of Epstein-Barr virus latent gene products in tumour cells of Hodgkin's disease. *Lancet* 337:320-322, 1991.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120, World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Spector BD, Filipovich AH, Perry GS, III, et al.: Epidemiology of cancer in ataxia-telangiectasia. pp.103-137. In *Ataxia-telangiectasia—A Cellular and Molecular Link between Cancer, Neuropathology and Immune Deficiency*. (Bridges BA, Handen DG, eds.). New York: John Wiley and Sons Ltd, 1982.
- Torelli G, Marasca R, Luppi M, et al.: Human herpesvirus-6 in human lymphomas: Identification of specific sequences in Hodgkin's lymphomas by polymerase chain reaction. *Blood* 77:2251-2258, 1991.
- Vincent NJ, Greenwald P and Davies JNP: Extended epidemic of Hodgkin's disease in high school students. *Lancet* 1(711):1209-1211, 1971.
- Weiss LM, Movahed LA, Warnke RA, et al.: Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. *N Engl J Med* 320:502-506, 1989.
- Wright DH: Pathology of Hodgkin's disease: Anything new? pp. 2-13. In *New aspects in the diagnosis and treatment of Hodgkin's disease. Recent Results in Cancer Research*. Berlin, (Diehl V, Pfreundschuh M, Loeffler M, eds.). New York: Springer-Verlag, 1989.

Malignant tumors of the kidney account for 2 percent of all new cancers each year in the United States. In 1994, there were approximately 27,600 new cases of kidney cancer and about 11,300 deaths; 60 percent of both new cases and deaths occur in men (Ries et al., 1994).

Kidney

Joseph K. McLaughlin, Ph.D.*

Renal cell cancer and renal pelvis cancer account for 70 percent and 15 percent of the tumors, respectively, with the remainder being primarily composed of cancer of the ureter (8 percent) and urethra (4 percent) (Devesa et al., 1990). Renal cell cancers develop in the main area of the kidney (renal parenchyma), while renal pelvis cancers develop in the lower part of the kidney where urine collects and begins its journey to the bladder via the ureter.

Internationally, the incidence rates for kidney cancer are highest in European and Scandinavian countries and North America (Parkin et al., 1992). In the United States, the incidence rate per 100,000 for renal cell cancer is 8.4 among white men, 8.6 among black men, 3.7 among white women, and 5.6 among black women (Devesa et al., 1990). The incidence rates for renal pelvis and ureter cancers are much lower, averaging between 1 and 2 per 100,000 for men and women of both races. Since the early 1970s, incidence rates for renal cell cancer have been increasing an average of 2 percent per year, and 3 percent per year for renal pelvis and ureter cancers (Devesa et al., 1990). The five-year relative survival rate for patients with renal cell cancer is about 50 percent, but for those with renal pelvis and ureter cancers the rate is about 65 percent (McLaughlin et al., in press). Wilms' tumor of the kidney (nephroblastoma) is found only among young children and is discussed in another section of this book (see Childhood Cancers).

Renal cell, renal pelvis, and ureter cancers share a number of risk factors (McLaughlin et al., 1983, 1984, 1992). Cigarette smoking is causally linked to these tumors, although the association with renal pelvis and ureter cancers is much stronger (McLaughlin et al., 1992). Risk ratios ranging from 1.5 to 2.5 have been reported for cigarette smoking and renal cell cancer, while ratios of 2.5- to 7-fold have been reported for renal pelvis and ureter cancers (McLaughlin et al., in press). Approximately 30 percent of renal cell cancers among men and 24 percent among women are attributable to cigarette smoking, while about 70 percent of the renal pelvis and ureter cancers among men and 40 percent among women can be linked to smoking.

Abuse of analgesics (particularly phenacetin-containing pain relievers) has been causally linked to cancers of the renal pelvis and ureter in a number of studies (McLaughlin et al., in press; IARC, 1987). More recently, long-term use of phenacetin-containing analgesics has also been associated with an increased risk of renal cell cancer (McLaughlin et al., 1985; McCredie et al., 1988). However, similar

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Kidney

to cigarette smoking, the association with phenacetin-containing drugs is much stronger among patients with renal pelvis and ureter cancers than among renal cell cancer patients. In the United States, phenacetin-containing analgesics have not been available in over-the-counter preparations since the late 1970s. Recently, an increased risk of renal cell cancer has been reported for regular use of prescription diuretics (Yu et al., 1986; McLaughlin et al., 1988), but further research is needed before any firm conclusions can be drawn.

A consistent risk factor for renal cell cancer, found in virtually all studies, is that of high relative weight or obesity. Although early studies noted the association primarily among women, more recent studies have also found an increased risk among overweight men (McLaughlin et al., in press). The reason for this association is unknown, and obesity is not related to the other tumors of the kidney.

Beverages such as coffee, tea, and alcoholic drinks have not been found to be important risk factors for renal cell, renal pelvis, or ureter cancers (McLaughlin et al., in press). Dietary findings are sparse for these tumors, although some studies have reported renal cell cancer to be associated with increased meat consumption (McLaughlin et al., 1984; Madsen and Willett, 1990).

Occupation contributes little to the etiology of renal cell cancer, although some studies have found death from kidney cancer to be elevated among asbestos-exposed workers (Selikoff et al., 1979), and among coke-oven workers in steel plants (Redmond, 1983). Because of the relative rarity of cancers of the renal pelvis and ureter, there have been few occupational reports on these tumors.

Given our present knowledge, prevention of these cancers is best achieved by cessation of cigarette smoking. About one-third of renal cell cancers and more than one-half of renal pelvis and ureter cancers could be avoided by eliminating the use of tobacco.

REFERENCES

- Boring CC, Squires TS, Tong T: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Devesa SS, Silverman DT, McLaughlin JK, et al.: Comparison of the descriptive epidemiology of urinary tract cancers. *Cancer Causes and Control* 1:133-141, 1990.
- International Agency for Research on Cancer: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, vols 1 to 42. *IARC Monogr Eval Carcinog Risks* (suppl) 7:310-312, 1987.
- Maclure M and Willett W: A case-control study of diet and risk of renal adenocarcinoma. *Epidemiology* 1:430-440, 1990.
- McCredie M, Ford JM and Stewart JH: Risk factors for cancer of the renal parenchyma. *Int J Cancer* 42:13-16, 1988.
- McLaughlin JK, Blot WJ, Mandel JS, et al.: Etiology of cancer of the renal pelvis. *J Natl Cancer Inst* 71:287-291, 1983.
- McLaughlin JK, Mandel JS, Blot WJ, et al.: A population-based case-control study of renal cell carcinoma. *J Nat Cancer Inst* 72:275-284, 1984.
- McLaughlin JK, Blot WJ, Mehl ES, et al.: Relation of analgesic use to renal cancer: Population-based findings. *J Natl Cancer Inst Monogr* 69:217-222, 1985.
- McLaughlin JK, Blot WJ and Fraumeni JF Jr: Diuretics and renal cell cancer. *J Natl Cancer Inst* 80:378, 1988.
- McLaughlin JK, Silverman DT, Hsing AW, et al.: Cigarette smoking and cancers of the renal pelvis and ureter. *Cancer Res* 52:254-257, 1992.
- McLaughlin JK, Blot WJ, Devesa SS, et al: Renal cancer. In *Cancer Epidemiology and Prevention*. (Schottenfeld D and Fraumeni JF Jr, eds.). 2nd ed. (in press). New York: Oxford University Press.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Redmond CK: Cancer mortality among coke oven workers. *Environ Health Perspect* 52:67-73, 1983.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Selikoff IJ, Hammond EC and Seidman H: Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci* 330:91-116, 1979.
- Yu MC, Mack TM, Hanisch R, et al.: Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst* 77:351-35, 1986.

Leukemias

Martha S. Linet, M.D., M.P.H.*

The leukemias are a family of biologically diverse malignancies resulting from an abnormal change in an early form of one or a few blood cells that arise in the bone marrow. The abnormal leukemic cells progressively increase in number, and suppress growth of normal blood cells (Henderson, 1990). Clinical symptoms that result from loss of normal blood cell function include infections, fever, abnormal bruising or bleeding, and fatigue. Other symptoms are directly related to the progressive increase in the number of leukemic cells in the spleen, liver, or lymph nodes.

Five main types (and an increasing number of subtypes) of leukemia have been identified: acute lymphocytic leukemia (ALL), chronic myelocytic or granulocytic leukemia (CMH or CGL), acute myelocytic or acute nonlymphocytic leukemia (AML or ANLL), chronic lymphocytic leukemia (CLL), and adult T-cell leukemia (ATL) (Linet, 1985). Together these account for about 2.5 percent of the total annual cancer incidence in the United States and about one-third of cancers in children (Miller et al., 1993).

There are notable differences in age distribution by subtype. Acute lymphocytic, the most common childhood cancer in most Western countries, is low in incidence among black children in the U.S. and in Africa, and among Arab and Indian children (Kasisi et al., 1990; Linet and Devesa, 1991; Parkin et al., 1992). Chronic lymphocytic leukemia is almost nonexistent before age 30, then increases rapidly with age, except among Asians older than 50 (Finch and Linet, 1992; Parkin et al., 1992). AML is the subtype of highest incidence among young and middle-aged adults, with rates consistently higher in more developed countries and in urban areas (Cartwright and Staines, 1992; Parkin et al., 1992). Chronic myelocytic leukemia accounts for 1 to 3 percent of childhood leukemia, rises in adolescence, then increases more rapidly in early adulthood, although rates are lower than those for AML. Rates for all types of leukemia are higher among males than among females (Parkin et al., 1992), and among Caucasians than blacks, except for CML (Groves et al., in press).

Childhood leukemia death rates have dramatically decreased since the 1960s because of treatment advances (Linet and Devesa, 1991; Aoki et al., 1992). Increases in CLL among the elderly within the past few decades have been attributed to improvements in diagnosis (Finch and Linet, 1992), whereas increases in AML among men 50 years and older in industrialized regions may reflect occupational exposures (Sandler and Collman, 1987).

Numerous families have been described in which two or more closely related members have been diagnosed with leukemia or related blood malignancy (Linet, 1985; Finch and Linet, 1992). In several large series of leukemia patients, 5 to 10 percent have reported additional close relatives with leukemia or related blood malignan-

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Leukemias

cies compared with 1 to 2 percent of similarly affected families of healthy persons (Pottern et al., 1991). Children with Down's syndrome or other abnormal chromosome condition are at increased risk of developing leukemia (Robison and Neglia, 1987). Most acute leukemia cases have been found to have chromosomal abnormalities (Sandler and Collman, 1987). The genetic or environmental factors responsible for familial occurrence or chromosome changes in individual leukemia patients are unknown, although chromosome abnormalities in a few cases have been linked with exposure to ionizing (X-rays or gamma rays) radiation, benzene, other solvents, pesticides, or to treatment with certain types of chemotherapy drugs (Sandler and Collman, 1987).

Excessive leukemia deaths were reported among early U.S. (Matanoski et al., 1984) and British radiologists (Smith and Doll, 1981) with high radiation exposures, but, because of lower doses and the use of shielding, no excess has occurred for several decades. Most studies of nuclear industry or shipyard workers have shown either no leukemia excess or small nonsignificant increases (National Research Council, 1990; Kendall et al., 1992). Some studies of nuclear industry workers have shown a positive dose-response relationship (Wilkinson and Dreyer, 1991; Kendall et al., 1992), while others have shown no association between radiation exposure level and leukemia risk (Fraser et al., 1993). Leukemia mortality was elevated among British (Darby et al., 1988) and New Zealand military (Pearce et al., 1990), but not among most U.S. servicemen (Robinette et al., 1985), participating in atmospheric nuclear tests.

Japanese children and adults exposed to high radiation levels experienced an increased leukemia risk (except for CLL) that peaked about five years subsequent to the atomic bomb blasts in Hiroshima and Nagasaki (National Research, 1990; Preston et al., 1994). Children born to women pregnant at the time of the blasts in Japan did not develop an elevated occurrence of leukemia, although an excess has been observed among children born and residing in proximity to Sellafield nuclear reprocessing plant in Great Britain despite very low measured radiation levels; the excess was observed among children and persons under age 25 before 1983 but not after that year (Draper et al., 1993). Some studies have shown leukemia increases among children whose fathers were employed in the nuclear industry (Gardner et al., 1990; Roman et al., 1993), but others have reported no increases (Kinlen et al., 1993). Numerous studies in Utah of a possible relationship of leukemia with fallout from nuclear weapons have been conflicting (Machado et al., 1987; Stevens et al., 1990). No increase in childhood or adult leukemia mortality was found in 113 U.S. counties adjacent to 62 nuclear plants compared with death rates in control counties (Jablon et al., 1991), nor have childhood leukemia excesses been identified to date in studies of cancer registries in European countries subsequent to the

Leukemias

accident in 1986 at the nuclear plant in Chernobyl in the former Soviet Union (Parkin et al., 1993; Auvinen et al., 1994; Hjalmarsson et al., 1994).

A 50 percent increase in childhood leukemia has generally been associated with pregnancy-related diagnostic X-ray exposure (MacMahon, 1962), but a few studies in children and studies examining the relationship of diagnostic X-ray exposure in adults with leukemia have been conflicting (Gibson et al., 1976; Boice et al., 1991). Radiotherapy treatments have been associated with leukemia excess among patients with ankylosing spondylitis (Darby et al., 1987), and with small increases among women with cervical and uterine cancer (Boice et al., 1987), heavy menstrual bleeding due to benign conditions (Luskipp et al., 1990), breast cancer (Curtis et al., 1992), and Hodgkin's disease (Tucker et al., 1988), although splenectomy may play a role in the latter (Tura et al., 1993). Children radiated for fungal infection of the scalp (Ron et al., 1988) or for large thymuses in infancy (Hildreth et al., 1985) have an elevated risk, although children treated for cancer with radiotherapy alone have not been found to develop increased leukemia (Tucker et al., 1987).

Electricians, power line workers, and electronics and other workers thought to be exposed to nonionizing electrical and magnetic fields have been reported to have an elevated leukemia (primarily AML) risk in some but not all studies in which assessment of occupational exposure was based on job titles (Savitz and Calle, 1987). A large study of Canadian and French utility workers demonstrated a small excess of AML (Theriault et al., 1994). Childhood leukemia has also been weakly linked with proxy measures of residential exposure to magnetic fields in some, but not all, studies (National Radiological Protection Board, 1992).

Benzene-exposed shoe, leather, rubber, and chemical manufacturing workers have been repeatedly shown to have excess leukemia (primarily AML that is two- to ten-fold increased) (IARC, 1981). Elevated leukemia risks have also occurred among some rubber manufacturing (Deltzell and Monson, 1981), petroleum refinery, and chemical plant workers (Wong and Raabe, 1989), and some pressmen and printers (Paganini-Hill, 1980), painters (Matanoski et al., 1986), and various other occupational groups. Small excesses have also been found among farmers in some regions; suspect exposures include certain livestock (e.g., viruses associated with poultry and dairy cows), pesticides, and other agrichemicals (Blair et al., 1992). Childhood leukemia has been linked in some studies with parental hydrocarbon-related, chemical or metal manufacturing, and other occupational exposures (Savitz and Chen, 1990). Interview data collected on environmental pesticide exposures after birth have also been associated with childhood leukemia in two studies (Lowengart et al., 1987; Shu et al., 1988), and are currently being evaluated as causes of leukemia in the first investigations with measurements of residential pesticide levels.

Leukemias

A possible association between cigarette smoking and adult leukemia was first suggested in 1986. Since then, follow-up studies in different U.S. populations have shown elevated risk of leukemia, particularly myeloid leukemia (Brownson et al., 1993; Siegel, 1993). Some studies comparing acute myeloid leukemia cases with controls have also shown this link (Brownson et al., 1993), although others and an earlier follow-up investigation of British doctors (Doll et al., 1976) have shown no excess of AML among smokers.

Despite considerable interest for decades in apparent leukemia clusters, results of multiple investigations have been inconclusive (Linnet, 1985; Cartwright and Staines, 1992). Viruses were long suspected (because of their known role in causing leukemia and related blood malignancies in animals), but the first human leukemia virus (a retrovirus called HTLV-I) was not identified until 1980. Since then, HTLV-I has been closely linked with a rare adult T-cell leukemia that clusters in southern Japan, the Caribbean, parts of Africa, and in immigrants from these regions to the United States. Approximately 2 to 12 percent of healthy persons in these areas show evidence of viral infection; among the infected individuals, lifetime risk of adult T-cell leukemia is 1 to 4 percent. The virus is spread through transfusion, by intravenous drug abuse, sexual intercourse, and breast-feeding (Blattner, 1993).

Leukemia has also been inconclusively linked with several immune-related diseases (Cartwright and Staines, 1992; Finch and Linnet, 1992). It is often not clear whether the associations of leukemia with previous nonmalignant diseases are due to the illness, to increased medical attention (resulting in increased diagnostic X-ray exposure and/or earlier diagnosis), or to drug treatments used for that condition. Unfortunately, AML has been consistently linked with a class of effective, important chemotherapy drugs called alkylating agents, which have been successfully used to treat many types of cancer as well as certain nonmalignant conditions (Pedersen-Bjergaard and Philip, 1989). Despite the known leukemia-causing effect of these drugs, equally effective alternatives for treating certain life-threatening cancers have yet to be identified. A few reports have also suggested that chloramphenicol (Shu et al., 1988), growth hormone (Fradkin et al., 1993) and others may be associated with leukemia, but definitive evidence is lacking.

Although numerous epidemiologic studies have assessed possible risk factors for the leukemias, the etiology of most cases is largely unknown. To date, lifestyle, diet, and most residential environmental exposures have received little attention.

REFERENCES

- Aoki K, Kurihara M, Hayakawa N, et al.: Death Rates for Malignant Neoplasms for Selected Sites by Sex and Five-Year Age Group in 33 countries: 1953-57 to 1983-87. pp. 503-536. Nagoya: University of Nagoya Press, 1992.
- Auvinen A, Hakama M, Arvola H, et al.: Fallout from Chernobyl and incidence of childhood leukaemia in Finland, 1976-92. *BMJ* 309:151-154, 1994.
- Blair A, Zahm SH, Pearce NE, et al.: Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 18:209-215, 1992.
- Blattner WA: Human T-cell lymphotropic viruses and cancer causation. In *Cancer: Principles and Practice of Oncology* (DeVita VT, Hellman S, Rosenberg SA, eds.). Philadelphia: J.B. Lippincott, 1993.
- Boice JD Jr, Blattner M, Kleinerman RA, et al.: Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst* 79:1295-1311, 1987.
- Boice JD Jr, Morin MM, Glass AG, et al.: Diagnostic X-rays and risk of leukemia, lymphoma, and multiple myeloma. *JAMA Assoc* 265:1290-1294, 1991.
- Brownson RC, Novotny TE, and Perry MC: Cigarette smoking and adult leukemia. A meta-analysis. *Arch Intern Med* 153:169-175, 1993.
- Cartwright RA, Staines A: Acute leukaemias. In *Epidemiology of Haematological Disease, Part I* (AF Fleming, ed.). London: Bailliere Tindal, 1992.
- Curtis RE, Boice JD Jr, Stovall M, et al.: Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* 326:1745-1751, 1992.
- Darby SC, Doll R, Gill SR, et al.: Long-term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. *Br J Cancer* 55:179-190, 1987.
- Darby SC, Kendall GM, Fell TP, et al.: A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmers. *Br Med J* 296:332-338, 1988.
- Delzell E and Monson RR: Mortality among rubber workers. III. Cause-specific mortality, 1940-1978. *J Occup Med* 23:677-684, 1981.
- Doll R and Peto R: Mortality in relation to smoking: 20 year observations on male British physicians. *BMJ* 2:1525-1536, 1976.
- Draper GJ, Stiller CA, Cartwright RA, et al.: Cancer in Cumbria and in the vicinity of the Sellafield nuclear installation, 1963-1990. *BMJ* 306:89-94, 1993.
- Finch SC and Linet MS: Chronic leukaemias. In *Epidemiology of Haematological Disease, Part I* (AF Fleming, ed.). London: Bailliere Tindal, 1992.
- Fradkin JE, Mills JL, Schonberger LB, et al.: Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 270:2829-2832, 1993.
- Fraser P, Carpenter L, Maconochie N, et al.: Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946-1986. *Br J Cancer* 67:615-621, 1993.
- Gardner MJ, Snee MP, Hall AJ, et al.: Results of a case-control study of leukemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *BMJ* 300:123-131, 1990.
- Gibson E, Graham S, Lilienfeld A, et al.: Epidemiology of diseases in adult males with leukemia. *J Natl Cancer Inst* 56:891-898, 1976.
- Groves FD, Linet MS and Devesa SS: Patterns of occurrence of the leukemias. *Am J Cancer* (in press).
- Henderson ES: Definition and classification. pp. 13-15. In *Leukemia*, 5th Edition. (Henderson ES and Lister TA, eds.). Philadelphia: W.B. Saunders Co., 1990.
- Hildreth NG, Shore RE, Hempelman LH, et al.: Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. *Radiat Res* 102:378-391, 1985.
- Hjalmar U, Kulldorf M, Gustafsson G, and the Swedish Child Leukaemia Group: Risk of acute childhood leukaemia in Sweden after the Chernobyl reactor accident. *BMJ* 309:154-157, 1994.
- Inskip PD, Monson RR, Wagoner JK, et al.: Leukemia following radiotherapy for uterine bleeding. *Radiat Res* 122:107-119, 1990.
- International Agency for Research on Cancer: Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Wood, Leather, and Some Associated Industries, vol 25. Lyon, IARC, 1981, 1-97.
- Jablons S, Hrubec Z and Boice JD, Jr: Cancer in populations living near nuclear facilities. *JAMA Assoc* 265:1403-1408, 1991.

- Kabat GC, Augustine A and Hebert JR: Smoking and adult leukemia: a case-control study. *J Clin Epidemiol* 42:907-914, 1988.
- Kasili EG: Childhood leukaemia: Is it a problem in tropical Africa? *Leuk Lymph* 1:187-193, 1990.
- Kendall GM, Muirhead CR, MacGibbon BH, et al.: Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *BMJ* 304:220-225, 1992.
- Kinlen LJ, O'Brien F, Clarke K, et al.: Rural population mixing and childhood leukaemia. Effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. *BMJ* 306:743-748, 1993.
- Linnet MS: The Leukemias: Epidemiologic Aspects. New York: Oxford University Press, 1985.
- Linnet MS and Devesa SS: Descriptive epidemiology of childhood leukaemia. *Br J Cancer* 63:424-429, 1991.
- Linnet MS and Devesa SS: Descriptive epidemiology of the leukemias. In *Leukemia*, 5th ed. (Henderson ES and Lister TA, eds.). Philadelphia: W.B. Saunders, 1990.
- Lowengart RA, Peters JM, Ciccioni C, et al.: Childhood leukemia and parents' occupational and home exposures. *J Natl Cancer Inst* 79:39-46, 1987.
- Machado SG, Land CE and McKay FW: Cancer mortality and radioactive fallout in southwestern Utah. *Am J Epidemiol* 125:44-61, 1987.
- MacMahon B: Prenatal X-ray exposure and childhood cancer. *J Natl Cancer Inst* 28:1173-1191, 1962.
- Matanoski GM, Sartwell P, Elliott E, et al.: Cancer risks in radiologists and radiation workers. pp. 83-96. In *Radiation Carcinogenesis: Epidemiology and Biological Significance*. (Boice JD Jr, Fraumeni JF Jr, eds.). New York: Raven Press, 1984.
- Matanoski GM, Stockwell HG, Diamond EL, et al.: A cohort mortality study of painters and allied tradesmen. *Scand J Work Environ Health* 12:16-21, 1986.
- Miller BA, Ries LAG, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1990. NIH Publ. No. 93-2789. Bethesda, MD, 1993.
- National Radiological Protection Board: Electromagnetic Fields and the Risk of Cancer. Report of an Advisory Group on Non-Ionising Radiation. vol 1, no. 1. Chilton, Didcot, Oxon, United Kingdom: National Radiological Protection Board, 1992.
- National Research Council Committee on the Biologic Effects of Ionizing Radiation: The Effects on Populations of Exposure to Low levels of Ionizing Radiation (BEIR V). Washington, DC: National Academy Press, 1990.
- Paganini-Hill A, Glazer E, Henderson BE, et al.: Cause-specific mortality among newspaper web pressmen. *J Occup Med* 22:542-544, 1980.
- Parkin DM, Cardis E, Masuyer E, et al.: Childhood leukaemia following the Chernobyl accident. The European Leukaemia-Lymphoma Incidence Study (ECLIS). *Eur J Cancer* 29A:87-95, 1993.
- Parkin DM, Muir CS, Whelan SL, et al.: Cancer Incidence in Five Continents, vol VI. Lyon, France: IARC Scientific Publication No. 120, 1992.
- Pearce N, Prior I, Methven D, et al.: Follow-up of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific. *BMJ* 300:1161-1166, 1990.
- Pedersen-Bjergaard J and Philip P: Therapy-related malignancies: a review. *Eur J Haematol* 42 (suppl 48):39-47, 1989.
- Pottern LM, Linnet MS and Blair A: Familial cancers associated with subtypes of leukemia and non-Hodgkin's lymphoma. *Leuk Res* 15:305-314, 1991.
- Preston D, Kusumi S, Tomonaga M, et al.: Cancer incidence in A-bomb survivors. Part III: Leukemia, lymphoma, and multiple myeloma, 1950-87. *Radiat Res* 137 (suppl): 68-97, 1994.
- Robinette CD, Jablon S and Preston TL: Mortality of Nuclear Weapons Test Participants. Medical Followup Agency, National Research Council. Washington, DC: National Academy Press, 1985.
- Robison LL and Neglia JP: Epidemiology of Down syndrome and childhood acute leukemia. pp. 19-32. In *Oncology and Immunology of Down Syndrome*. (McCoy EE, Epstein CJ, eds.) New York: Alan Liss, 1987.
- Roman E, Watson A, Beral V, Buckle S, et al.: Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in West Berkshire and North Hampshire health districts. *BMJ* 306:615-621, 1993.
- Ron E, Modan B and Boice JD Jr: Mortality after radiotherapy for ringworm of the scalp. *Am J Epidemiol* 127:713-725, 1988.
- Sandler DP and Collman GW: Cytogenetic and environmental factors in the etiology of the acute leukemias in adults. *Am J Epidemiol* 126:1017-1032, 1987.

- Savitz DA and Calle EE: Leukemia and occupational exposure to electromagnetic fields: Review of epidemiologic surveys. *J Occup Med* 29:763-773, 1987.
- Savitz DA and Chen J: Parental occupation and childhood cancer: A review of epidemiologic studies. *Environ Health Perspect* 88:325-337, 1990.
- Shu X-O, Gao Y-T, Brinton LA, et al.: A population-based case-control study of childhood leukemia in Shanghai. *Cancer* 62:635-644, 1988.
- Siegel M: Smoking and leukemia: evaluation of a causal hypothesis. *Am J Epidemiol* 138:1-9, 1993.
- Smith PG and Doll R: Mortality from cancer and all causes among British radiologists. *Br J Radiol* 54:187-194, 1981.
- Stevens W, Thomas DC, Lyon JL, et al.: Leukemia in Utah and radioactive fallout from the Nevada test site. *JAMA* 264:585-591, 1990.
- Theriault G, Goldberg M, Miller AB, et al.: Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970-1989. *Am J Epidemiol* 139:550-572, 1994.
- Tucker MA, Coleman CN, Cox RS, et al.: Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med* 318:76-81, 1988.
- Tucker MA, Meadows AT and Boice JD Jr: Leukemia after therapy with alkylating agents for childhood cancer. *J Natl Cancer Inst* 78:459-464, 1987.
- Tura S, Fiacchini M, Zinzani PL, et al.: Splenectomy and the increasing risk of secondary acute leukemia in Hodgkin's disease. *J Clin Oncol* 11:925-930, 1993.
- Wilkinson GS and Drever NA: Leukemia among nuclear workers with protracted exposure to low-dose ionizing radiation. *Epidemiol* 2:305-309, 1991.
- Wong O and Raabe GK: Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site. *Am J Ind Med* 15:283-310, 1989.

Liver

Primary liver cancer refers to any malignant tumor arising in the liver itself, rather than originating elsewhere and spreading—or metastasizing—to the liver. The most common forms of primary liver cancer are hepatocellular carcinoma and cholangiocarcinoma, which arise from the liver cells and the bile ducts respectively. Other tumors may arise in the liver from cells that are found throughout the body, such as angiosarcoma (from the lining cells of blood vessels), and lymphoma (from white blood cells) (Okuda, 1986).

Although hepatocellular carcinoma is one of the most common tumors worldwide, it remains relatively uncommon in the industrialized countries of the Western world. The highest world standardized incidence rates were noted for Khon Kaen, Thailand, and Quidong, China, with rates of 90 per 100,000. By contrast, United States rates were less than 5 per 100,000 (Parkin et al., 1992). There were about 16,000 cases of primary liver cancer in the United States in 1994.

Hepatocellular carcinoma is unusual in that the causative factor can often be identified in individual patients, whereas in other common forms of cancer (such as colon or breast cancer), only broad categories of risk can be identified. Hepatitis B virus, which is the most important factor in the occurrence of hepatocellular carcinoma worldwide, is endemic in those regions where hepatocellular carcinoma is most common (Szmuness, 1978). While some patients have been followed from detection of chronic hepatitis B infection to the development of hepatocellular carcinoma years or even decades later, not all patients with chronic hepatitis B develop tumors. People from the Far East and Africa tend to acquire hepatitis B infection at birth or in early childhood, while in the United States it is usually contracted in adulthood. It is usually necessary for infection with hepatitis B to occur early in life in order for hepatocellular carcinoma to develop; it rarely develops in individuals who become infected in adulthood (Tabot, 1991). Males are at much greater risk (two- to seven-fold higher) for developing hepatocellular carcinoma than females. Finally, patients with cirrhosis of the liver resulting from hepatitis B are at much higher risk of developing hepatocellular carcinoma than those patients with less severe liver disease.

Other causative factors have been identified for hepatocellular carcinoma, the most common of which is cirrhosis of any cause. Cirrhosis refers to the consequences of chronic liver injury, i.e., extensive scarring of the liver in which the scar tissue surrounds “nodules” of regenerating liver tissue. The causes of cirrhosis include alcohol abuse, chronic hepatitis, prolonged obstruction to the outflow of bile from the liver, and some viral forms of autoimmune liver disease.

Recently, infection with the hepatitis C virus has been strongly linked with hepatocellular carcinoma. Hepatitis C is a very common form of hepatitis. Reports from Italy and Spain initially identified a large proportion of patients with hepatocellular

Adrian Di Bisceglie, M.D.,
F.A.C.S.^a, and
Edward Tabor, M.D.^b

^a From the Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

^b From the Division of Cancer Etiology Biological Carcinogenesis Program, National Cancer Institute, Bethesda, Maryland

Liver

carcinoma who tested positive in serum antibody to the hepatitis C virus (Colombo, 1989). Studies from Japan have shown that hepatocellular carcinoma often arises in patients with chronic liver disease attributed to hepatitis C (Lisker-Melman et al., 1989). Hepatocellular carcinoma has doubled in incidence in Japan during the past 25 years; all of the increase is attributable to hepatitis C virus-associated cases (Nishioka et al., 1991).

Exposure to some chemicals and toxins can lead to hepatocellular carcinoma. Perhaps the best known and extensively studied of these is aflatoxin, produced by a common mold that infests poorly stored peanuts and other foods. Dietary contamination with aflatoxin has been a particular problem in some underdeveloped countries in Africa and the Far East. Aflatoxin readily causes liver cancer in laboratory animals and, in man, may potentiate the cancer-causing effects of hepatitis B infection (Ross et al., 1992). However, the extent of its role as a cause of hepatocellular carcinoma in humans is not known.

Several reports of hepatocellular carcinoma occurring in users of oral contraceptives and anabolic steroids have linked the use of steroids to the development of this malignancy. Because of the relatively small numbers of patients involved, this link has been very difficult to confirm (Hsing et al., 1992).

Whether or not smoking increases the risk of hepatocellular carcinoma remains controversial. Some studies suggest that smoking may be a more important cause of hepatocellular carcinoma in the Western countries where hepatitis B is less common (Hsing et al., 1990).

Finally, the question of whether or not alcohol, by itself, causes hepatocellular carcinoma is undecided. While hepatocellular carcinoma often arises in the presence of alcoholic cirrhosis, it is not known whether the underlying cirrhosis or the alcohol itself predisposes to cancer. Alcohol use can increase the risk of hepatocellular carcinoma due to hepatitis B virus; a similar role in hepatitis C virus-associated hepatocellular carcinoma has not been observed (Shimizu et al., 1992; Ikeda et al., 1993).

Some forms of inherited metabolic diseases may predispose to hepatocellular carcinoma (Lisker-Melman et al., 1989). By far the most common of these is hemochromatosis, a disorder of iron metabolism which results in an excessive accumulation of iron in the body. This iron accumulation will eventually lead to cirrhosis if it is not treated and the cirrhosis again provides the right environment for the development of hepatocellular carcinoma. Other, rarer, metabolic diseases that are sometimes linked to hepatocellular carcinoma include tyrosinemia, glycogen storage disease, and alpha-1-antitrypsin deficiency.

REFERENCES

- Colombo M, Kuo G, Choo QL, et al.: Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* 2:1006-8, 1989.
- Hsing AW, Hoover RN, McLaughlin JK, et al.: Oral contraceptives and primary liver cancer among young women. *Cancer Causes and Control* 3:43-48, 1992.
- Hsing AW, McLaughlin JK, Hrubec Z, et al.: Cigarette smoking and liver cancer among U.S. veterans. *Cancer Causes and Control* 1:217-221, 1990.
- Ikeda K, Saito S and Koida I: A multivariate analysis of risk factors for hepatocellular carcinogenesis: A prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology* 18, 47-53, 1993.
- Kato Y, Nakata K, Omagari K, et al.: Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. *Cancer* 74:2234-2238, 1994.
- Lisker-Melman M, Martin P and Hoofnagle JH: Conditions associated with hepatocellular carcinoma. *Med Clin North Am* 73:999-1009, 1989.
- Nishioka K, Watanabe J, Furuta S, et al.: A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. *Cancer* 67:429-433, 1991.
- Okuda K: Primary liver cancer. Quadrennial Review Lecture. *Dig Dis Sci* 31:133S-146S, 1986.
- Parkin DM, Muir CS, Whelan S, et al.: Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Ross RK, Yuan JM, Yu MC, et al.: Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 339:943-946, 1992.
- Shimizu S, Kiyosawa K, Sodeyama T, et al.: High prevalence of antibody to hepatitis C virus in heavy drinkers with chronic liver disease in Japan. *J Gastroenterol Hepatol* 7:30-35, 1992.
- Szmuness W: Hepatocellular carcinoma and the hepatitis B virus: Evidence for a causal association. *Prog Med Virol* 24:40-69, 1978.
- Tabor E: Strongly supported features of the association between hepatitis B virus and hepatocellular carcinoma. In *Etiology, Pathology, and Treatment of Hepatocellular Carcinoma in North America*, pp. 107-117. Portfolio: The Woodlands, Texas, 1991.

Lung and Larynx

Jay H. Lubin, Ph.D.*

Primary lung cancer accounts for about 15 percent of all cancer cases (19 percent in males and 11 percent in females) in the United States; however, because of its high death rate, it accounts for 29 percent of all cancer deaths—35 percent in males and 21 percent in females (Boring et al., 1994). The overall 5-year relative survival rate is only 13 percent (Ries et al., 1994).

Lung cancer remains the leading cause of cancer death in most countries. Maoris of New Zealand experienced the highest incidence rate in the world among males, with a world standardized rate of 119.1 per 100,000 (Parkin et al., 1992). U.S. black men were near the highest, with an incidence rate of 90.0 per 100,000. Low rates were noted for Israel, India, and Latin American countries.

The worldwide incidence of lung cancer is substantially lower in females—a difference generally attributed to lighter tobacco consumption by women, although other factors may play a role. For example, high levels of indoor and outdoor air pollution have been postulated as an important contributor to the high rates of lung cancer among females in China, whose smoking prevalence is relatively low (Blot and Fraumeni, 1992).

In the United States, lung cancer incidence has risen more sharply in females (4.6 percent annual change) than in males (0.5 percent annual change) in recent years, reflecting the growing popularity of cigarette smoking among females over the past several decades (Ries et al., 1994). Currently, more women die each year from lung cancer than breast cancer (Boring et al., 1994).

Although overall age-adjusted mortality rates of lung cancer continue to rise in the United States, rates have begun to decline for those under the age of 45 (Devesa et al., 1989). The decrease is greatest among white men, but a decrease among black men and white and black women has also occurred. If trends continue, overall lung cancer mortality rates will start to decline among men in the 1990s and among women after the year 2000.

Cigarette smoking is the major cause of lung cancer. The link was first suspected in the 1920s and 1930s, and today, after multiple case-control and cohort studies, the overwhelming evidence is documented in more than 20 reports of the U.S. Surgeon General. Smoking is currently estimated to cause 85 percent of all lung cancer deaths. Lung cancer mortality increases with increasing dose, as determined by number of cigarettes smoked daily, smoking duration, and inhalation patterns. The risk of dying from lung cancer is 22 times higher among male smokers and 12 times higher among female smokers than among people who have never smoked (U.S. DHHS, 1990).

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Lung and Larynx

Cessation of smoking reduces the risk of death from lung cancer; after ten years the risk of lung cancer death among former smokers is about 50 percent of the risk of continuing smokers (U.S. DHHS, 1990). Those who reduce their daily usage and those who smoke filtered, low-tar cigarettes gain some benefit, although they still have lung cancer risks much higher than nonsmokers (Lubin et al., 1984).

Environmental tobacco smoke (ETS) has been determined to increase the risk of lung cancer in nonsmokers. This conclusion, presented in both the 1986 U.S. Surgeon General's Report (U.S. DHHS 1986) and a Report of a Committee of the National Academy of Sciences (NAS 1988), was based on a variety of evidence including more than 20 epidemiologic studies, as well as laboratory analyses which show the components of sidestream smoke to be qualitatively similar to mainstream smoke. Evidence suggests that persons exposed to ETS are subjected to a lung cancer risk equivalent to smoking 0.1 to 1.0 cigarettes per day.

Increased risk of lung cancer has also been associated with the smoking of pipes and cigars, but at a lower level of risk than that for cigarettes. This may be due to a less intense pattern of smoking, with cigar and pipe smokers typically inhaling less deeply and less frequently.

Radon is an inert gas produced by the radioactive decay of radium and uranium. While concentrations of these elements vary widely, they are found everywhere in the crustal rock of the earth. Radon itself is radioactive and may cause lung cancer. Studies of underground miners exposed to radon have consistently shown an increased risk of lung cancer with greater cumulative exposure to radon and its short-lived decay products (Lubin et al., 1994; NAS, 1988; Samet 1989). The results of these studies, together with animal studies, suggest that radon exposure is a cause of lung cancer, at least at levels historically found in mines.

Radon may also enter homes by migrating from the earth through cracks in the foundation, or through the hole for a sump pump, or, in rare cases, via private water wells, by dissolving in drinking water. Although the radon concentration in some homes may reach levels found in mines, average domestic cumulative lifetime exposure to radon is about 5 to 15 times lower than for miners. Based on miner studies, it has been estimated that radon may cause 6,000–24,000 lung cancer deaths each year in the United States (Lubin and Boice, 1989). However, because of uncertainties in using miner-based results, the precise public health consequences of domestic exposure to radon is currently an important unresolved issue. Results of ecologic studies and case-control studies, using either indirect estimates of personal exposure or direct measurements of indoor radon concentrations, have been mixed in showing an association between radon level in the home and lung cancer risk (Samet 1989).

Lung and Larynx

Studies of occupational groups have identified several other respiratory carcinogens, although it is difficult to assess their overall public health impact. Some of these exposures—such as radon—may be widespread in the population but at very low levels, while other exposures may have their greatest impact on subgroups of the population, as with asbestos exposure among shipyard workers. It should be noted that the carcinogenic effect of some of these exposures, e.g., asbestos, is enhanced by tobacco smoke.

Exposure to airborne asbestos appears to be the largest cancer threat in the workplace, raising the risk of lung cancer and mesothelioma (a cancer that arises in the lining of the chest cavity, or mesothelium) as well as asbestosis, a lung disease (Blot and Fraumeni, 1992). The risk of developing these three diseases is substantially higher for workers in a number of asbestos industries, including miners and millers, and textile, insulation, shipyard, and cement workers. Lung cancer is the major asbestos-related disease, and accounts for death in about 20 percent of some men exposed to asbestos for long periods of their work life (Selikoff et al., 1979). Even men who worked for short periods in shipyards during World War II have a higher risk of developing lung cancer than workers never exposed to asbestos (Blot et al., 1978; 1980).

Lung cancer is also one of the major effects of high doses of ionizing radiation. Excesses of lung cancer have been reported among some patients who received radiation therapy, and among atomic bomb survivors in Japan (Beebe et al., 1978), where both gamma rays and neutrons were released.

A number of other occupational agents contribute to the incidence of lung cancer: mustard gas, chloromethyl ethers, chromium, nickel, and inorganic arsenic.

Air pollution has been suspected as a cause of lung cancer, but it has been difficult to establish definite links. Of special concern are the effects of the byproducts of the combustion of fossil fuels, most notably polycyclic aromatic hydrocarbons (PAHs). Studies have suggested that exposure to benzo(a)pyrene may increase lung cancer risk. In both urban and rural areas of China, exceptionally high levels of indoor air pollutants from the use of coal for heating and for cooking, along with cigarette use, have been implicated in the high rate of lung cancer (Mumford et al., 1987; Xu et al., 1989). Although suggestive, the association of lung cancer and PAHs has not yet been conclusively demonstrated, as other components of air pollution may also be carcinogenic.

Lung and Larynx

Finally, there is laboratory evidence of a protective effect against lung cancer with increased intake of vitamins A (retinol and precursor carotenes), C, E, selenium, and other micronutrients. Epidemiologic studies have provided support for some of these associations. The clearest and most consistent associations occur with the consumption of fresh fruits and vegetables. Studies show that risk of lung cancer was reduced by as much as 50 percent among those with the greatest compared to those with the least consumption of these foods (Blot and Fraumeni, 1992). The precise component responsible is still uncertain, but most attention has been focused on carotenoids, particularly beta-carotene.

Approximately 12,500 new cases of cancer of the larynx, or voicebox, occur each year, 9,800 in males and 2,700 in females (Boring et al., 1994). It has an incidence pattern similar to that of cancers of the mouth and throat, occurring more often among men than women and more often among blacks than among whites. The annual incidence of laryngeal cancer among U.S. white men is 7.8 cases per 100,000 population, and 1.7 among white women. Among black men, the annual incidence is 13.0 per 100,000, and 2.7 among black women (Ries et al., 1994).

In the United States between 1973 and 1991, the incidence of laryngeal cancer declined 0.6 percent annually in white males, but increased 1.6 percent in white females over the same time. In blacks, the annual incidence increased in both sexes, 0.9 percent in males and 2.3 percent in females (Ries et al., 1994).

Risk factors for laryngeal cancer include tobacco, alcohol, asbestos, and nickel and mustard gas exposure. As with cancers of the lung, mouth, and throat, many cases of laryngeal cancer can be attributed to cigarette smoking. Cigarette smokers have almost a ten-fold greater risk for laryngeal cancer than do nonsmokers, and risk increases with increased cigarette smoking (Wynder et al., 1982). Not only is heavy alcohol consumption a risk factor, but tobacco and alcohol together appear to act synergistically.

REFERENCES

- Beebe GW, Kato H and Land CE: Studies of the mortality of A-bomb survivors, #6. Mortality and radiation dose, 1950-1974. *Radiat Res* 75:138-201; 1978.
- Blot WJ and Fraumeni JF Jr: Lung and pleura. In *Cancer Epidemiology and Prevention*, 2nd ed. (Schottenfeld D and Fraumeni JF Jr, eds.). Philadelphia: WB Saunders, 1992.
- Blot WJ, Harrington JM, Toledo A, et al.: Lung cancer after employment in shipyards during World War II. *N Engl J Med* 299:620-624; 1978.
- Blot WJ, Morris LE, Stroube R, et al.: Lung and pharyngeal cancers in relation to shipyard employment in coastal Virginia. *J Natl Cancer Inst* 65:571-575; 1980.
- Boring CC, Squires FS and Tong T: Cancer Statistics 1991. *CA Cancer J Clin* 41:7-26, 1991.
- Devesa SS, Blot WJ and Fraumeni JF Jr: Declining lung cancer rates among young men and women in the United States: a cohort analysis. *J Natl Cancer Inst* 81:1568-1571, 1989.
- Hammond EC, Selikoff IJ and Seidman H: Asbestos exposure, cigarette smoking and death rates. *Ann NY Acad Sci* 330:473-490, 1979.
- Lubin JH, Blot WJ, Berrino F, et al.: Modifying risk of developing lung cancer by changing habits of cigarette smoking. *Br Med J* 288:1953-1956, 1984.
- Lubin JH and Boice JD Jr: Estimating radon-induced lung cancer in the U.S. *Health Physics* 57:117-127, 1989.
- Lubin JH, Boice JD Jr, Edling C, et al.: Radon and lung cancer risk: a joint analysis of 11 underground miners studies. National Cancer Institute, NIH Publ. No. 94-3614, Bethesda, MD, 1994.
- Mumford JL, He XZ, Chapman RS, et al.: Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 235:217-220, 1987.
- National Academy of Sciences: Report of the Committee on the Biological Effects of Ionizing Radiation: Health effects of radon and other internally deposited alpha emitters. Washington, DC: National Academy Press, 1988.
- National Academy of Sciences: Report of the Committee on the Biological Effects of Ionizing Radiation: Health effects of exposure to low levels of ionizing radiation. Washington, DC: National Academy Press, 1990.
- Parkin DM, Muir CS, Whelan S, et al. (eds.): *Cancer Incidence in Five Continents*, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs. National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Samet JM: Radon and lung cancer. *J Natl Cancer Inst* 81:745-757, 1989.
- Selikoff IJ, Hammond EC and Seidman H: Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci* 330:91-116; 1979.
- U.S. Department of Health and Human Services: A Report of the Surgeon General: The Health Consequences of Involuntary Smoking. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health. DHHS Publ. No. (CDC) 87-8398, 1986.
- U.S. Department of Health and Human Services: A Report of the Surgeon General: The Health Benefits of Smoking Cessation. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publ. No. (CDC) 90-8416, 1990.
- Wynder EL and Hoffmann D: Tobacco. In *Cancer Epidemiology and Prevention* (Schottenfeld D and Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders, 1982.
- Xu ZX, Blot WJ, Xiao HP, et al.: Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst* 81:1800-1806; 1989.

Melanoma is a cancer of the cells that produce and transport the pigment melanin. In the United States, approximately 32,000 new cases of skin melanoma were projected for 1994 (Boring et al., 1994). Melanomas can occur on any skin surface, but in light-skinned populations, a clear excess occurs on the trunk in men, the lower extremities in women, and the head and neck regions and arms in both sexes. In dark-skinned populations, melanomas occur most often on the palms of the hands and the soles of the feet.

The highest melanoma rates occur among light-skinned populations in areas of intense sunlight, e.g., Arizona and Queensland, Australia (World Health Organization et al., 1990). In the United States, data for whites from the NCI Surveillance, Epidemiology, and End Results (SEER) Program show an incidence rate of 12.4 and a mortality rate of 2.5 per 100,000 (Ries et al., 1994). Mortality rates within the United States vary inversely with latitude (Pickle et al., 1987).

Over the last several decades, the incidence of melanoma has increased dramatically in the United States and several other countries, posing a major threat to public health (Devesa et al., 1987; Glass and Hoover, 1989; Ries et al., 1994). In the United States, the reported incidence for whites rose 102 percent from 1973 to 1991. The increase for white males was 124 percent. This rate of increase leads all other cancers, including lung cancer in females. The increase has been most marked in older white males and females. The exact pattern of increase is not certain, because of underreporting, as suggested by higher rates measured in an HMO than in the general population (Glass and Hoover, 1989). For the period 1987 to 1991, the rate of increase, in whites, measured in SEER population registries slowed to 1.8 percent per year (Ries et al., 1994). Nevertheless, there is growing concern that the depletion of the earth's ozone layer and the subsequent increase in the amount of ultraviolet radiation (UVR) reaching the earth may exacerbate the increase in melanoma incidence in the next several decades (Longstreth, 1987).

Melanoma represents only about 5 percent of all skin cancers in the United States, but it accounts for about 75 percent of all skin cancer deaths, about 6,900 deaths per year (Boring et al., 1994). Survival rates have been increasing because more melanomas are being diagnosed at an early stage. For white patients diagnosed between 1983 to 1990, the overall relative 5-year survival rate was 85 percent. Despite a better survival percentage, the total mortality rate continues to increase because of the dramatic increase in incidence.

Melanoma of the Skin

Mary C. Fraser, R.N., M.A.*,
and Patricia Hartge, Sc.D.*

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Melanoma of the Skin

Although the precise cause of melanoma is unknown, numerous clinical and epidemiologic studies in the past decade have identified characteristics associated with increased risk of melanoma: a history of sunburns, fair skin, number of moles, presence of dysplastic or other atypical moles, previous melanoma, family history of melanoma, and immunosuppression. Several recent review articles discuss them in greater detail (Rhodes et al., 1987; Evans et al., 1988; MacKie et al., 1989; Koh, 1991; Fraser et al., 1991; and Elwood, 1993).

Sunlight Exposure

Melanoma is related to excessive exposure to ultraviolet radiation (UVR), but not so directly as are the more common nonmelanoma skin cancers, basal cell carcinoma, and squamous cell carcinoma. Most nonmelanoma skin cancers are related to chronic overexposure to UVR, while melanoma appears to be related to intense intermittent exposure to UVR, especially in early life. Several recent studies have found significantly increased risks of melanoma following repeated severe (blistering) sunburns, particularly during childhood and teenage years. Inconsistent associations have been reported with regard to the influence of constant long-term exposure to sun.

Fair Skin

People with fair skin and light eyes and hair experience sun sensitivity because they have less melanin, which protects their skin from the cumulative damage produced by UVR. The fact that these people suntan minimally, or not at all, and sunburn easily presumably explains the high risk among lightly pigmented individuals. Freckles, an indicator of sun sensitivity and sun damage, are associated with increased risk.

Mole Characteristics

Mole patterns, including type and number of moles, are an important risk factor. Most moles (nevi), which are clusters of melanocytes, are benign lesions called common acquired nevi. Rarely, a mole may undergo abnormal changes, and if it is not removed, become a melanoma. Alternatively, some melanomas arise in a skin site where there was not a preexisting mole. A persistently changed or changing mole, particularly in an adult, may be the most important risk factor for the development of melanoma (Rhodes et al., 1987).

Melanoma of the Skin

Dysplastic nevi identify individuals at increased risk of melanoma, both in the familial and nonfamilial setting. Dysplastic nevi are different from common acquired moles in that they are often larger than normal moles (>6mm, the size of a pencil eraser), have irregular and indistinct borders, have a flat component, and often contain shades of pink, red, and brown. The risk of melanoma is highest for members of melanoma-prone families who have dysplastic nevi and who have already had a melanoma; they are at exceedingly high risk of developing additional primary melanomas (Tucker, 1988). Members of melanoma-prone families with dysplastic nevi but no personal history of melanoma are also at greatly increased risk of melanoma. The risk of melanoma among persons with dysplastic nevi but no family history of either melanoma or dysplastic nevi is increased, but is not nearly so high as in those with a family history of melanoma.

Giant congenital nevi, which are present at birth or develop within the first year of life, are a risk factor for melanoma (Rhodes et al., 1987). The risk of melanoma associated with small congenital nevi is more controversial.

Other Risk Factors

Individuals who have already had one melanoma also have increased risk of developing additional primary melanomas (Rhodes et al., 1987; Evans et al., 1988; Tucker, 1988; MacKie et al., 1989; Koh, 1991; Fraser et al., 1991). People with a family history of melanoma, even without dysplastic nevi, have increased risk. Certain states of immunosuppression are associated with increased risk, e.g., renal transplant recipients and Hodgkin's disease. Individuals with xeroderma pigmentosum, a rare hereditary skin disease, lack an enzyme that normally repairs cellular DNA damaged by UVR and face increased risk of both melanoma and non-melanoma skin cancers. In addition, significantly elevated risks of melanoma are seen after brain and breast cancer (Tucker, 1988). The increase of melanoma after breast cancer may relate to shared hormonal or reproductive risk factors.

Oral contraceptives were once proposed as a risk factor, but numerous subsequent studies have found no association. Other factors that have been studied and generally found unrelated to risk include: alcohol, caffeine, tobacco, hair dyes, pesticides, marital status, and parity. Fluorescent lighting has been proposed as a risk factor, but has not been extensively studied. Dietary constituents may play a role, but no consistent associations have emerged to date. Similarly, no occupational hazards, apart from UVR exposures, have been identified.

REFERENCES

- Boring CC, Squires TS and Tong T: Cancer Statistics 1991. *CA Cancer J Clin* 41:7-26, 1991.
- Devesa S, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947-1984. *J Natl Cancer Inst* 79:701-770, 1987.
- Elwood JM: Recent developments in melanoma epidemiology, 1993. *Melanoma Research* 3:149-156, 1993.
- Evans RD, Kopf AW, Lew RL, et al: Risk factors for the development of malignant melanoma—I: Review of case-control studies. *J Dermatol Surg Oncol* 14:393-408, 1988.
- Fraser MC, Hartge P and Tucker MA: Melanoma and non-melanoma skin cancer: Epidemiology and risk factors. *Semin Oncol Nurs* 7:2-12, 1991.
- Glass AG and Hoover RN: The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 262:2097-2100, 1989.
- Koh HK: Cutaneous melanoma (medical progress). *N Engl J Med* 325:171-182, 1991.
- Longstreth JD, ed.: Ultraviolet radiation and melanoma with a special focus on assessing the risks of stratospheric ozone depletion. Vol 4 of *Assessing the Risks of Trace Gases that can Modify the Stratosphere*. Washington, DC: Environmental Protection Agency, 1987.
- Mackie RM, Freudenberger F and Aitchison TC: Personal risk-factor chart for cutaneous melanoma. *Lancet* 2:487-490, 1989.
- Rhodes AR, Weinstock MA, Fitzpatrick TB, et al: Risk factors for cutaneous melanoma. A practical method for recognizing predisposed individuals. *JAMA* 258:3146-3151, 1987.
- Ries LAG, Miller BA, Hankey BF, et al: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs. National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1991.
- Tucker MA: Individuals at high risk of melanoma. In *Pigment Cell*, vol 9 (Mackie RM, ed.). Basel, Switzerland: S. Karger, 1988, 95-109.
- Whelan SL, Parkin DM and Masuyer E (eds.): *Patterns of Cancer in Five Continents*, p. 29. World Health Organization, International Agency for Research on Cancer, and International Association of Cancer Registries. IARC Scientific Publication No. 102, Lyon, 1990.

Multiple myeloma is a cancer of the plasma cells that are usually found in the bone marrow. These cells produce immunoglobulins or antibodies that normally circulate in the blood and help ward off disease. The main characteristic of the malignant plasma cell is the excess production and growth of a specific immunoglobulin type or a subunit of the immunoglobulin.

Multiple Myeloma

Linda M. Pottern,
M.P.H., Ph.D.*

Multiple myeloma patients typically seek medical attention because of intermittent bone pain. Characteristic bone lesions seen by X-ray examination accounts for the name "multiple" myeloma and for the earlier classification of this disease as a bone cancer. Other clinical symptoms commonly include anemia, kidney failure, and increased susceptibility to infection.

In 1994, an estimated 12,700 new cases of multiple myeloma were diagnosed in the United States (Boring et al., 1994). Multiple myeloma primarily affects older individuals. In the United States, the median age at onset is 67 for blacks and 71 for whites (Ries et al., 1994). Multiple myeloma is one of the few cancers that occurs twice as frequently in blacks as in whites. The annual incidence for 1987–91 was 11.1 cases per 100,000 for black men and 7.7 for black women, compared with 5.1 for white men and 3.3 for white women (Ries et al., 1994). U.S. blacks experienced the highest incidence of multiple myeloma in the world, while Asians and Hispanics had low rates (Parkin et al., 1992).

The prognosis for multiple myeloma is generally poor. Based on cases diagnosed from 1983 to 1990, U.S. blacks had a slightly higher five-year relative survival rate than whites, 29 percent and 27 percent, respectively (Ries et al., 1994).

Little is known about the etiology of multiple myeloma. Both environmental and genetic factors may play a role in the development of this cancer (Riedel et al., 1992). Exposure to ionizing radiation has been linked with multiple myeloma. The strongest associations have been noted for Japanese atomic bomb survivors (Shimizu, 1990), U.S. radiologists (Matanoski et al., 1975), and radium dial workers (Stebbins et al., 1984). Nuclear power plant workers may also be at an increased risk for developing multiple myeloma (Darby et al., 1988; Gilbert et al., 1989). Living near nuclear facilities, however, does not appear to be associated with myeloma occurrence (Jablon et al., 1990).

Numerous epidemiologic studies have reported a link between multiple myeloma and farming or agricultural work (Riedel et al., 1992). However, it is not clear whether pesticides, agricultural exhausts, chemicals, dusts, or a combination of these exposures are the responsible agents. Other nonspecific occupational exposures that have been associated with myeloma include metals, rubber, wood,

* From the Biostatistics Branch,
Division of Environmental
Epidemiology, National Cancer
Institute, Bethesda, Maryland

Multiple Myeloma

leather, paint, and petroleum (Riedel et al., 1992). Workplace exposure to benzene, a chemical used in many manufacturing processes, may play a role in the development of multiple myeloma (Decoufle et al., 1983; Rinsky et al., 1987).

It has been a longstanding belief that prolonged stimulation of the immune system by repeated infections, allergic conditions, or autoimmune disease may increase the risk of myeloma. The current scientific evidence is weak. A few studies have reported elevated myeloma risks with specific medical conditions such as allergies, rheumatoid arthritis, and rheumatic fever, while other studies have not found these or other such associations (Riedel et al., 1992).

The occurrence of multiple myeloma among siblings, spouses, and family members of myeloma patients suggests that genetic factors and common environmental exposures play a role in the development of this cancer (Riedel et al., 1992). The discovery of specific human leukocyte antigens (HLA) (Leech, 1983; Pottern et al., 1992), chromosome abnormalities (Lewis and MacKenzie, 1984; Nishida et al., 1989) and oncogenes (Ernst et al., 1988; Gould et al., 1988; Selvanavagam et al., 1988) among myeloma patients adds further support for a genetic predisposition for this cancer.

A link between cigarette smoking and myeloma has been suggested in a recent study (Mills et al., 1990); however, this association has not been shown in other studies (Gallagher et al., 1983; Flodin et al., 1987; Linet et al., 1987; Brown et al., 1992; Heineman et al., 1992). Other lifestyle factors, such as dietary patterns and alcohol consumption, have yet to be fully explored in epidemiologic investigations of multiple myeloma.

REFERENCES

- Boring CC, Squires TS and Tong T, Montgomery S: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Brown LM, Everett GD, Gibson R, et al.: Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. *Cancer Causes Control* 3:49-55, 1992.
- Darby SC, Kendall GM, Fell TP, et al.: A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapons tests and experimental programmes. *Br Med J* 296:332-338, 1988.
- Decoufle P, Blattner WA and Blair A: Mortality among chemical workers exposed to benzene and other agents. *Environ Res* 30:16-25, 1983.
- Ernst TJ, Gazdar A, Ritz J, et al.: Identification of a second transforming gene, *ras*, in a human multiple myeloma line with a rearranged *c-myc* allele. *Blood* 72:1163-1167, 1988.
- Flodin U, Fredriksson M and Persson B: Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-referent study. *Am J Ind Med* 12:519-529, 1987.
- Gallagher RP, Spinelli JJ, Elwood JM, et al.: Allergies and agricultural exposure and risk factors for multiple myeloma. *Br J Cancer* 48:853-857, 1983.
- Gilbert ES, Petersen GR and Buchanan JA: Mortality of workers at the Hanford Site: 1945-1981. *Health Physics* 56:11-25, 1989.
- Gould J, Alexanian R, Goodacre A, et al.: Plasma cell karyotype in multiple myeloma. *Blood* 71:453-456, 1988.
- Heineman EF, Zahm SH, McLaughlin JK, et al.: A prospective study of tobacco use and multiple myeloma: evidence against an association. *Cancer Causes Control* 3:31-36, 1992.
- Jablon S, Hrubec Z, Boice JD, Jr, et al.: Cancer in populations living near nuclear facilities. DHHS Publ. No. (NIH) 90-874. Washington, DC: U.S. Govt Print Off, 1990.
- Leech SH, Bryan CF, Elston RC, et al.: Genetic studies in multiple myeloma. I. Association with HLA-Cw5. *Cancer* 51:1408-1411, 1983.
- Lewis JP and MacKenzie MR: Non-random chromosomal aberrations associated with multiple myeloma. *Hematol Oncol* 2:307, 1984.
- Linet MS, Harlow SD and McLaughlin JK: A case-control study of multiple myeloma in whites: Chronic antigenic stimulation, occupation, and drug use. *Cancer Res* 47:2978-2981, 1987.
- Matanoski GM, Seltser R, Sartwell PE, et al.: The current mortality rates of radiologists and other physician specialists: Specific causes of death. *Am J Epidemiol* 101:199-210, 1975.
- Mills PK, Newell GR, Beeson WL, et al.: History of cigarette smoking and risk of leukemia and myeloma: results from the Adventist Health Study. *J Natl Cancer Inst* 82:1832-1836, 1990.
- Nishida K, Taniwaki M, Misawa S, et al.: Nonrandom rearrangement of chromosome 14 at band q32.33 in human lymphoid malignancies with mature B-cell phenotype. *Cancer Res* 49:1275-1281, 1989.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Pottern LM, Gart JJ, Nam J, et al.: HLA and multiple myeloma among black and white men: Evidence of a genetic association. *Cancer Epidebm Biomarkers Prevent* 1:177-182, 1992.
- Riedel D and Pottern LM: The epidemiology of multiple myeloma. In *Hematology/Oncology Clinics of North America*, vol 6 (Barlogie B, ed.). Philadelphia: W.B. Saunders, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Rinsky RA, Smith AB, Hornung R, et al.: Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med* 316:1044-1050, 1987.
- Selvanayagam P, Blick M, Narni F, et al.: Alteration and abnormal expression of the *c-myc* oncogene in human multiple myeloma. *Blood* 71:30-35, 1988.
- Shimizu Y, Kato H and Schull WJ: Studies of the mortality of A-bomb survivors. Report 9. Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). *Radiat Res* 121:120, 1990.
- Stebbing JH, Lucas HF and Stehney AF: Mortality from cancers of major sites in female radium dial workers. *Am J Ind Med* 5:435-459, 1984.

Non-Hodgkin's Lymphoma

Sheila Zahm, Ph.D.*

Lymphomas are cancers that affect the white blood cells of the immune system. They are characterized by the abnormal growth of lymphocytes, the infection-fighting cells in the lymph nodes, spleen, and thymus. The tonsils, stomach, small intestine, and skin may also be affected. Primary lymphomas of the skin such as mycosis fungoides and Sezary's disease are extremely rare. Burkitt's lymphoma, rare in most of the world, is the most common childhood cancer in Central Africa, and is one of the most aggressive of all human cancers.

Lymphomas are usually classified as Hodgkin's disease or non-Hodgkin's lymphoma. An estimated 45,000 new cases of non-Hodgkin's lymphoma were diagnosed in the United States in 1994 (Boring et al., 1994). Incidence per 100,000 is 18.6 among white males, 12.0 among white females, 12.8 among black males, and 8.1 among black females. In the United States, five-year survival is 53 percent for white patients and 45 percent for black patients. The highest incidence rates internationally for non-Hodgkin's lymphoma were observed for the United States and Canada (Parkin et al., 1992), although comparing incidence, survival, and mortality statistics among countries may be difficult because of differing classification systems used for these diseases.

Between 1973 and 1991, the 73 percent increase in the incidence of non-Hodgkin's lymphoma was one of the largest among the major cancer sites in the United States (Ries et al., 1994). Part of the increase in incidence of non-Hodgkin's lymphoma in recent years has been related to AIDS. Non-Hodgkin's lymphoma is about 60 times more common in AIDS patients than in the general U.S. population (Beral et al., 1991). Gail et al. (1991) estimated that between 8 and 27 percent of all non-Hodgkin's lymphoma cases that occurred in the United States in 1992 were a direct consequence of infection with human immunodeficiency virus (HIV). AIDS, however, cannot explain the increase in non-Hodgkin's lymphoma observed over a period that began years before the AIDS epidemic surfaced, and continues to be observed in the absence of HIV infection.

Other immunodeficiency states, both genetic and induced by medications or illness, are also associated with extremely high risks of non-Hodgkin's lymphoma (Filipovich et al., 1992; Kinlen, 1992). Kidney transplant patients, whose immune systems are suppressed with medications, develop non-Hodgkin's lymphomas 40 to 100 times more frequently than expected (Fraumeni and Hoover, 1977; Kinlen et al., 1979). As an alternative mechanism, immunostimulation may play a role in the high risks observed in some groups with immune abnormalities (Hoover, 1992).

Viruses other than HIV have also been linked to non-Hodgkin's lymphoma (Mueller et al., 1992). Human T-lymphotropic virus, type I (HTLV-I) has been linked to certain types of adult T-cell leukemias and lymphomas found mostly in

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Non-Hodgkin's Lymphoma

southern Japan, parts of the Caribbean and Africa, and the southeastern United States (Mueller, 1991), but is not a likely factor in the widespread increase in non-Hodgkin's lymphoma. On the other hand, Epstein-Barr virus (EBV) is ubiquitous—by adulthood almost everyone has been exposed to it and has developed antibodies against it. EBV has been linked to Burkitt's lymphoma in African children (Ziegler, 1981) and is linked to non-Hodgkin's lymphoma in persons with acquired or genetic immunosuppression (Mueller et al., 1992). Its role in non-Hodgkin's lymphoma in the general population is under investigation.

Pesticides have been associated with non-Hodgkin's lymphoma in studies of farmers, other pesticide applicators, manufacturing workers and other exposed populations (Zahm and Blair, 1992). One study, conducted in Kansas, revealed a striking association between non-Hodgkin's lymphoma and the use of herbicides, particularly 2,4-D (Hoar et al., 1986). The risk of non-Hodgkin's lymphoma rose with increasing frequency of use of herbicides, rising almost eight-fold among 2,4-D-using farmers who handled herbicides 20 or more days per year. Another study conducted in Nebraska also found a significantly increasing risk of non-Hodgkin's lymphoma with increasing use of 2,4-D, although the risks were lower than observed in Kansas (Zahm et al., 1990). Associations between non-Hodgkin's lymphoma and herbicides were also found in Sweden (Hardell et al., 1981) and Canada (Wigle et al., 1990) and with chlorophenols in Sweden (Hardell et al., 1979). Canine malignant lymphoma has also been associated with dog owner use of 2,4-D and commercial pesticide lawn treatments (Hayes et al., 1991). Grain handlers exposed to pesticides, grain dusts, and organic solvents have been found to have a five-fold risk of non-Hodgkin's lymphoma (Alavanja et al., 1990). Exposure to organophosphate insecticides may also play a role in the development of non-Hodgkin's lymphoma (Zahm et al., 1990; Cantor et al., 1992). Risks to the general population, who are exposed at much lower levels than occupationally exposed groups, have not been well studied.

Occupations other than agriculture that have been associated with non-Hodgkin's lymphoma include rubber workers (Monson and Nakano, 1976; Wilcosky et al., 1984), petroleum refining workers (Delzell et al., 1988), vinyl chloride workers (Chiazze et al., 1977), chemists (Li et al., 1969; Searle, 1978; Olin and Ahlbom, 1980), dry cleaners (Blair et al., 1990), and aircraft maintenance workers (Spirtas et al., 1991). The etiologic agents responsible for these excesses have not been identified definitively, but the occupations have in common exposure to organic solvents.

Non-Hodgkin's Lymphoma

Hair dye use, particularly long-term use of dark-color products, and occupational exposure to hair coloring products were associated with lymphatic and hematopoietic malignancies, including non-Hodgkin's lymphoma, in several recent studies (Cantor et al., 1988; Zahm et al., 1992; Thun et al., 1994; Linos et al., 1994; Giles et al., 1984). Hair-coloring products contain compounds that are mutagenic, carcinogenic, and teratogenic in animals. While there was no or little increased risk reported for overall use of hair coloring products, long-term dark-product users experienced two- to four-fold increased risk in some studies. The role of hair coloring products in the etiology of these malignancies, however, remains controversial (Zahm et al., 1994; Colditz 1994; Thun et al., 1994). The studies that reported the excesses were not conducted to investigate hair-coloring products as their primary focus, and so the questionnaires lack detail that is critical to judging causality. It is important to resolve the questions about the possible carcinogenicity of hair-coloring products. Approximately 35 to 60 percent of women and 10 percent of men use hair-coloring products (Zahm et al., 1994; Zahm et al., 1992), and use appears to be rising in young people (Sturgeon and Hartge, submitted).

In summary, the incidence of non-Hodgkin's lymphoma has been rising inexplicably. A continued, perhaps even larger, increase is anticipated because of AIDS-related cases. The cofactors that predispose AIDS cases to lymphoma need elucidation and research is needed into other possible causes of non-Hodgkin's lymphoma, such as hair-coloring products, pesticides, nitrates, solvents, other industrial chemicals, and viruses other than HIV.

REFERENCES

- Alavanja MC, Blair A and Masters MN: Cancer mortality in the U.S. flour industry. *J Natl Cancer Inst* 82:840-848, 1990.
- Beral V, Peterman T, Berkelman R, et al.: AIDS-associated non-Hodgkin lymphoma. *Lancet* 337:805-809, 1991.
- Blair A, Stewart PA, Tolbert P, et al.: Cancer and other causes of death among a cohort of dry cleaners. *Br J Ind Med* 47:162-168, 1990.
- Boring CC, Squires TS, Tong T, et al.: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Cantor KP, Blair A, Everett G, et al.: Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 52:2447-2455, 1992.
- Cantor KP, Blair A, Everett G, et al.: Hair dye use and risk of leukemia and lymphoma. *Am J Public Health* 78:570-571, 1988.
- Chiazze L Jr, Nichols WE and Wong O: Mortality among employees of PVC fabricators. *J Occup Med* 19:623-628, 1977.
- Colditz GA: Response to "Hair coloring products: Safe or still suspect?" *J Natl Cancer Inst* 86:943, 1994.
- Delzell E, Austin H and Cole P: Epidemiologic studies of the petroleum industry. *Occup Med, State of the Art Reviews* 3:455-474, 1988.
- Filipovich AH, Mathur A, Kamat D, et al.: Primary immunodeficiencies: Genetic risk factors for lymphoma. *Cancer Res* 52 (suppl):5465s-5467s, 1992.
- Fraumeni JF Jr and Hoover R: Immunosurveillance and cancer: Epidemiologic observations. *J Natl Cancer Inst Monogr* 47:121-126, 1977.
- Gail MH, Pluda JM, Rabkin CS, et al.: Projections of the incidence of non-Hodgkin's lymphoma related to acquired immunodeficiency syndrome. *J Natl Cancer Inst* 83:695-701, 1991.
- Giles GG, Lickiss JN, Baikie MJ, et al.: Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972-80: Occupational and familial aspects. *J Natl Cancer Inst* 72:1233-1240, 1984.
- Hardell L and Sandstrom A: Case-control study: Soft-tissue sarcoma and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer* 39:711-717, 1979.
- Hardell L, Eriksson M, Lenner P, et al.: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. *Br J Cancer* 43:169-176, 1981.
- Hayes HM, Tarone RE, Cantor KP, et al.: Case-control study of canine malignant lymphoma: Positive association with dog owner's use of 2,4-dichlorophenoxyacetic acid herbicides. *J Natl Cancer Inst* 83:1226-1231, 1991.
- Hoar SK, Blair A, Holmes FF, et al.: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 256:1141-1147, 1986.
- Hoover RN: Lymphoma risks in populations with altered immunity—a search for mechanism. *Cancer Res* 52 (suppl):5477s-5478s, 1992.
- Kinlen L: Immunosuppressive therapy and acquired immunological disorders. *Cancer Res* 52 (suppl):5474s-5476s, 1992.
- Kinlen LJ, Shiel AGR, Peto J, et al: Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 2:1461-1466, 1979.
- Li FP, Fraumeni JF Jr, Mantel N, et al.: Cancer mortality among chemists. *J Natl Cancer Inst* 43:1159-1164, 1969.
- Linos A, Kiamouris C, Foukanelis T, et al.: A case-control study of non-Hodgkin's lymphoma (abstract). *Am J Epidemiol* 139:S46, 1994.
- Monson RR and Nakano KK: Mortality among rubber workers. I. White male union employees in Akron, Ohio. *Am J Epidemiol* 103:284-296, 1976.
- Mueller N: The epidemiology of HTLV-I infection. *Cancer Causes and Control* 2:37-52, 1991.
- Mueller NE, Mohar A and Evans A: Viruses other than HIV and non-Hodgkin's lymphoma. *Cancer Res* 52 (suppl):5479s-5481s, 1992.
- Olin GR and Ahlbom A: The cancer mortality among Swedish chemists graduated during three decades. A comparison with the general population and with a cohort of architects. *Environ Res* 22:154-161, 1980.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.

- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Searle CE, Waterhouse JAH, Herman BA, et al.: Epidemiological study of the mortality of British chemists. *Br J Cancer* 38:192-193, 1978.
- Spiras R, Stewart PA, Lee JS, et al.: Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br J Ind Med* 48:515-530, 1991.
- Sturgeon SR and Hartge P: Trends in the use of hair coloring products among American men and women (submitted).
- Thun MJ, Altekruse SE, Namboodiri MM, et al.: Hair dye use and risk of fatal cancers in U.S. women. *J Natl Cancer Inst* 86:210-215, 1994.
- Thun MJ, Calle EE, Myers DG, et al.: Response to "Hair coloring products: Safe or still suspect?" *J Natl Cancer Inst* 86:943-944, 1994.
- Wigle DT, Semenciw RM, Wilkins K, et al.: Mortality study of Canadian male farm operators: Non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 82:575-582, 1990.
- Wilcosky TC, Checkoway H, Marshall EG, et al.: Cancer mortality and solvent exposures in the rubber industry. *Am Ind Hyg Assoc J* 45:809-811, 1984.
- Zahn SH and Blair A: Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 52 (suppl):5485s-5488s, 1992.
- Zahn SH, Blair A and Fraumeni JF, Jr: Hair coloring products: Safe or still suspect? *J Natl Cancer Inst* 86:941-943, 1994.
- Zahn SH, Weisenburger DD, Babbitt PA, et al.: A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1:349-356, 1990.
- Zahn SH, Weisenburger DD, Babbitt PA, et al.: Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. *Am J Public Health* 82:990-998, 1992.
- Ziegler JL: Burkitt's lymphoma. *N Engl J Med* 305:735-745, 1981.

Nearly 30,000 new cases of oral cancer—cancers of the lip, tongue, mouth, and pharynx—were estimated for the United States in 1994, and about 7,900 people died of the disease (Boring et al., 1994). These cancers account for almost 4 percent of all malignancies. Except for salivary gland tumors, which are rare, almost all oral cancers are squamous cell carcinomas and share a common etiology. Overall five-year relative survival for oral cancer has remained stable at 40 to 50 percent for several decades. Prognosis varies considerably according to the site of the tumor, stage of disease at treatment, gender, and the age of the patient.

In Americans, oral cancer is two to three times more common among males than females. Over 90 percent of cases occur in persons over age 45, with an average age of 64 for whites and 57 for blacks. Like most epithelial tumors, risk of oral cancer increases with age. This cancer occurs more frequently in blacks than whites. During 1987–91, the average annual age-adjusted incidence rate for oral cancer in the United States was 15.8 cases per 100,000 persons per year among white men, 6.2 among white women, 23.7 among black men, and 6.5 among black women (Ries et al., 1994). The most commonly involved sites are the tongue, floor of mouth, gum and other parts of the mouth, lip, tonsil (oropharynx), and hypopharynx. Among white males, the gums and the floor of the mouth are the most frequently affected sites. Among black males, the most common site is the pharynx, or throat. In this country, differences in alcohol and tobacco use account for the bulk of the racial differences in oral cancer (Day et al., 1993). The highest oral cancer rates in the world (world standardized rates > 40/100,000) are reported in parts of France, India, and Southeast Asia (Parkin et al., 1992).

Tobacco and alcohol account for approximately three-fourths of all oral cancers in the U.S. (Blot et al., 1988) and are the primary causes of these cancers in most Western countries (IARC 1986, 1988). In some parts of the country, smokeless tobacco use contributes to the high rates of gum and buccal cancers (Surgeon General, 1986). Recent epidemiologic evidence indicates that smoking and drinking are independent risk factors for oral cancer that produce a synergistic effect when combined. In the largest population-based case-control study of oral cancer yet conducted (Blot et al., 1988), strong positive trends in risk were observed according to amount and duration of each type of tobacco and for amount of alcohol consumption. Relative to nonsmokers, heavy cigarette smokers (40+/day for 20+ years) experienced a four-fold risk (men) and ten-fold risk (women) after adjusting for alcohol intake. After controlling for smoking, moderate drinkers (15–29 alcoholic drinks/week) had a three-fold risk of oral cancer and heavy drinkers (> 30 drinks/week) experienced an eight- to nine-fold risk. Combined heavy smoking and drinking resulted in a greater than 35-fold excess risk.

Oral Cavity and Pharynx

Gina L. Day, Ph.D.*

* From the Epidemiology and Extramural Programs Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Oral Cavity and Pharynx

The decline in risk of oral cancer following cessation of smoking is particularly rapid, providing further evidence of the role of smoking. In the study by Blot and coworkers, the risk of quitters was less than half that of continuing smokers five years following cessation of smoking, and little or no elevation in risk was found among those who had quit smoking for ten or more years. The chewing of quids containing betel leaves, tobacco, and lime and the smoking of bidi (a tobacco preparation rolled in betel leaf) contribute to the majority of cases in parts of India and Southeast Asia (Mahboubi and Sayed, 1982; Javant and Deo, 1986). In the southern United States, use of snuff is the primary cause of cancers arising in the cheek and gum (Winn et al., 1981). Among users of snuff, cancerous lesions typically arise at the site where smokeless tobacco, or quid, is held in contact with the buccal mucosa or gingiva. Although not as prevalent as cigarette smoking, habitual use of pipes, cigars, and smokeless tobacco is associated with relative risks for cancers of the mouth as great as that for cigarette smoking.

Among other potential etiologic factors, recent epidemiologic studies have indicated that diet may play an important role in the origins of these cancers. Findings have pointed to the protective effects of a diet consistently high in fresh fruits; vegetables; vitamins A, C, and E; and carotenoids, even with adjustment for alcohol intake and smoking (McLaughlin et al., 1988; Franco et al., 1989; Gridley et al., 1990; Franceschi et al., 1991; La Vecchia et al., 1991). A reduced risk of oral cancer associated with vitamin E supplementation has been shown in one study (Gridley et al., 1992). Poor dentition and oral hygiene, trauma due to ill-fitting dentures or jagged teeth, and use of mouthwashes high in alcohol content may enhance oral cancer risk (Winn et al., 1991). Iron deficiency anemia, a relatively common disorder, may produce atrophic oral changes (as seen in patients with Plummer-Vinson syndrome) that may predispose to malignant transformation. Certain generalized skin diseases, such as syphilis and erosive lichen planus, have been implicated as a contributory factor in the development of cancers of the tongue (Mahboubi and Sayed, 1982). DNA viruses, including human papillomaviruses and herpes simplex viruses, have been suggested as possible risk factors, but their role remains to be clarified (Maden, 1992).

Associations with other factors, such as urban residence, lower socioeconomic status, and social instability have been found (Greenberg et al., 1991); however, these factors are highly correlated with patterns of exposure to the major risk factors, tobacco and alcohol. Although some early studies have suggested that certain occupational groups, including textiles, metal, and steel workers, as well as persons exposed to asbestos and polyvinyl chloride, have a higher than expected rate of oral cancer (Mahboubi and Sayed, 1982), available epidemiologic evidence indi-

cates that the occupational component does not play a large role in oral cancer etiology. Outdoor work (or sunlight exposure) has been linked to lip cancer, and an increased risk of salivary gland tumors has been associated with ionizing radiation (Mahboubi and Sayed, 1982).

Oral leukoplakia is the most common precancerous lesion, with a small percent of such lesions ultimately becoming malignant. Oral cancer is also characterized by an exceptionally high incidence of subsequent tumors in the same site or adjacent sites in the upper digestive and respiratory tracts. Major determinants of new primaries following oral cancer are high levels of tobacco smoking and alcohol drinking (Day et al., 1994).

Based on available information, oral cancer is highly preventable. Quitting smoking and limiting alcohol intake would greatly limit deaths from this disease.

Oral Cavity and Pharynx

REFERENCES

- Blot WJ, McLaughlin JK, Winn DM, et al.: Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 48:3282-7, 1988.
- Boring CC, Squires TS, Tong T, et al.: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Day GL and Blot WJ: Second primary tumors in patients with oral cancer. *Cancer* 70:14-19, 1992.
- Day GL, Blot WJ, Austin DF, et al.: Racial differences in risk of oral and pharyngeal cancer: Alcohol, tobacco, and other determinants. *J Natl Cancer Inst* 85:165-173, 1993.
- Day GL, Blot WJ, Shore RE, et al.: Second cancers following oral and pharyngeal cancer: the role of tobacco and alcohol. *J Natl Cancer Inst* 86:131-137, 1994.
- Franceschi S, Bidoli E, Baron AE, et al.: Nutrition and cancer of the oral cavity and pharynx. *Int J Cancer* 40:20-25, 1991.
- Franco EL, Kowalski LP, Oliveira BV, et al.: Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer* 43:992-1000, 1989.
- Greenberg RS, Haber MJ, Clark WS, et al.: The relation of socioeconomic status to oral and pharyngeal cancer. *Epidemiology* 2:194-200, 1991.
- Gridley G, McLaughlin JK, Block G, et al.: Diet and oral and pharyngeal cancer among blacks. *Nutr Cancer* 14: 219-225, 1990.
- Gridley G, McLaughlin JK, Block G, et al.: Vitamin supplement use and reduced risk of oral and pharyngeal cancer. *Am J Epidemiol* 135:1083-1092, 1992.
- IARC (1986): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol 38, Tobacco Smoking, Lyon, 1986.
- IARC (1988): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol 41, Alcohol Drinking, Lyon, 1988.
- Jayant K and Deo MG: Oral cancer and culture practices in relation to betel quid and tobacco chewing and smoking. *Cancer Detect Prev* 9:207-213, 1986.
- La Vecchia C, Negri E, D'Avanzo B, et al.: Dietary indicators of oral and pharyngeal cancer. *Int J Epidemiol* 20:39-44, 1991.
- Maden C, Beckman AM, Thomas DB, et al.: Human papillomavirus, herpes simplex virus and the risk of oral cancer in men. *Am J Epidemiol* 135:1093-1102, 1992.
- Mahboubi E and Sayed GM: Oral Cavity and Pharynx, pp. 583-595. In *Cancer Epidemiology and Prevention* (Schottenfeld D, Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders, 1982.
- McLaughlin JK, Gridley G, Block G, et al.: Dietary factors in oral and pharyngeal cancer. *J Natl Cancer Inst* 80:1237-1243, 1988.
- Parkin DM, Muir CS, Whelan S, et al. (eds.): *Cancer Incidence in Five Continents*, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BE, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Surgeon General: *The Health Consequences of Using Smokeless Tobacco*. Department of Health and Human Services, NIH Publ. No. 86-2874, Bethesda, MD, 1986.
- Winn DM, Blot WJ, McLaughlin JK, et al.: Mouthwash use and oral conditions in the risk of oral and pharyngeal cancer. *Cancer Res* 51:3044-47, 1991.
- Winn DM, Blot WJ, Shy CM, et al.: Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 305:745-749, 1981.

Ovary

Patricia Hartge, Sc.D.*

The ovaries are a pair of almond-shaped glands that lie on each side of the uterus. They store egg cells and secrete the hormones that regulate pregnancy and menstruation. While cancers can occur in any of the multiple types of ovarian cells (Scully 1987), they typically arise in the layer of epithelial cells that surround the ovary. Left and right ovaries are affected about equally, and both are involved at the time of diagnosis in one-third of cases (Johannes, 1992).

In 1994, there were an estimated 24,000 new cases and 13,600 deaths from ovarian cancer in the United States (Boring et al., 1994). Since 1973, incidence has increased slightly while mortality has declined. The 1987–91 age-adjusted incidence was 14.8 cases per 100,000 women; the incidence increases with age until age 75 when rates decline (Ries et al., 1994). Five years after a diagnosis of ovarian cancer, survival is approximately 42 percent (Ries et al., 1994).

Scandinavian countries were among those reporting the highest ovarian cancer incidence rates in the world, with world standardized rates over 14/100,000 (Parkin et al., 1992). Comparable rates for U.S. white and black women, respectively, are 13 and 7 per 100,000 (Ries et al., 1994). Risk is also three to five times greater among women whose mothers or sisters have developed ovarian cancer (Amos et al., 1993) and, among women with a history of breast cancer, there is an estimated excess risk of 70 percent (Harvey and Brinton, 1985).

Several reproductive and menstrual factors affect the risk of developing ovarian cancer (Booth and Beral, 1985; Parazzini et al., 1991), the strongest being the number of full-term pregnancies (Whittemore et al., 1992a, 1992b). Women who have had three or four pregnancies have about half the risk of women who have had none; the average reduction in risk appears to be 13 to 19 percent per pregnancy. The number of incomplete pregnancies and the time spent breast-feeding are also associated with progressively decreasing risk, but are not as beneficial as term pregnancies. The time spent taking oral contraceptives strongly relates to risk, with a 5 to 10 percent additional reduction in risk for each year. The combined effect of family history, parity, and oral contraceptive use produce a 15-fold gradient in risk (Hartge et al., 1994). Women who have had difficulty getting pregnant are at increased risk, even after the other risk factors are taken into account.

Tubal ligation and hysterectomy clearly are associated with reduced risk, but the explanation remains uncertain (Weiss and Harlow, 1986). Use of talcum powder on the perineal area appears to be associated with risk, but accounts for few cases and there may not be a causal relationship (Harlow et al., 1992).

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Ovary

Several studies have found dietary fat to be associated with a slight increase in risk (Parazzini et al., 1991). One new dietary hypothesis proposes that, in people with a slower-than-normal galactose to glucose conversion time, a diet high in lactose poses an increased risk (Cramer et al., 1989). However, this theory has not been confirmed in subsequent studies (Herrington et al., 1995).

Reproductive and menstrual characteristics that apparently have little or no effect on risk include: age at first birth, age at menarche, age at menopause, and estrogen replacement therapy. Alcohol, coffee, and tobacco appear not to affect risk either (Hartge et al., 1989; Parazzini et al., 1991).

Epithelial tumors of low malignant potential have a different clinical appearance and course from invasive cancers, but their epidemiology appears to be quite similar (Harris et al., 1992; McGowan et al., 1988). Nonepithelial tumors show markedly different epidemiology; parity and oral contraceptive use may be associated with increased risk (Whittemore et al., 1992b).

REFERENCES

- Amos CI and Struwing JP: Genetic epidemiology of epithelial ovarian cancer. *Cancer* 71 (2 suppl):566-572, 1993.
- Booth M and Beral V: The epidemiology of ovarian cancer. In *Ovarian Cancer* (Hudson CN, ed.). Oxford: Oxford University Press, 1985.
- Boring CC, Squires TS and Tong T: Cancer Statistics 1994. *CA Cancer J Clin* 44:7-26, 1994.
- Cramer DW, Harlow BL, Willett WC, et al.: Galactose consumption and metabolism in relation to the risk of ovarian cancer. *Lancet* ii:66-71; 1989.
- Harlow BL, Cramer DW, Bell DA, et al.: Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 80(1):19-26, 1992.
- Hartge P, Whittemore AS, Itnyre J and the Collaborative Ovarian Cancer Group: Rates and risks of ovarian cancer in subgroups of white women in the United States. *Obstet Gynecol* 84:760-764, 1994.
- Harris R, Whittemore AS, Itnyre J, and the Collaborative Ovarian Cancer Group: Characteristics relating to ovarian cancer risk: Collaborative analysis of twelve U.S. case-control studies. III. Epithelial tumors of low malignant potential in white women. *Am J Epidemiol* 136(10):1204-11, 1992.
- Hartge P, Schiffman MH, Hoover R, et al.: A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol* 161:10-16, 1989.
- Harvey EB and Brinton LA: Second cancer following cancer of the breast in Connecticut, 1935-82. *J Natl Cancer Inst Monogr* 68:99-112, 1985.
- Johannes CB, Kaufman DW, Rosenberg L, et al.: Site of origin of epithelial ovarian cancer. *BMJ* 304(6818): 27-28, 1992.
- McGowan L, Norris HJ, Hartge P, et al.: Risk factors in ovarian cancer. *Eur J Gynaecol Oncol* 9:195-199, 1988.
- Parkin DM, Muir CS, Whelan S, et al. (eds.): *Cancer Incidence in Five Continents*, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Parazzini F, Franceschi S, La Vecchia C, et al.: The epidemiology of ovarian cancer. *Gynecol Oncol* 43:9-23, 1991.
- Ries LAG, Miller BA, Hankey BF, et al.: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*, National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Scully RE: Classification of human ovarian tumors. *Environ Health Perspect* 73:15-24, 1987.
- Stanford JL: Oral contraceptives and neoplasia of the ovary. *Contraception* 43:543-556, 1991.
- Weiss NS and Harlow BL: Why does hysterectomy without bilateral oophorectomy influence the subsequent incidence of ovarian cancer? *Am J Epidemiol* 124:856-858, 1986.
- Whittemore AS, Harris R, Itnyre J, and the Collaborative Ovarian Cancer Group: Characteristics relating to ovarian cancer risk: Collaborative analysis of twelve U.S. case-control studies. II. Invasive epithelial cancers in white women. *Am J Epidemiol* 136(10):1184-203, 1992a.
- Whittemore AS, Harris R, Itnyre J, and the Collaborative Ovarian Cancer Group: Characteristics relating to ovarian cancer risk: Collaborative analysis of twelve U.S. case-control studies. IV. The pathogenesis of epithelial ovarian cancer. *Am J Epidemiol* 136(10):1212-20, 1992b.

Pancreas

Roni Falk, M.S.*

The pancreas, an organ about six inches long located behind the stomach, has two functions: to send insulin into the bloodstream to control the amount of sugar in the blood and to send pancreatic juice into the intestine to help digest food. Cancer usually occurs in the small tubes or ducts in the organ which transport the pancreatic juice.

Cancer of the pancreas is a "silent" disease that occurs in an inaccessible part of the body, remaining asymptomatic until well advanced. Characteristically, pancreatic cancer presents with pain, biliary obstruction, clinical wasting (10 percent or more of normal body weight by the time of diagnosis), and early subclinical metastases. To date, only a biopsy will yield a certain diagnosis. Survival is poor; only about 3 percent of patients are alive five years after diagnosis (Ries et al., 1994).

Pancreatic cancer ranks 11th in incidence of all cancers in the United States, but is the fifth most common cause of cancer death (Falk et al., 1988). From the early 1950s through the mid-1970s, incidence rates for pancreatic cancer in the United States rose nearly 30 percent, quite possibly the result of improved diagnostic techniques. Thereafter, rates decreased slightly for males and remained unchanged for females. Mortality rates showed similar trends, reaching 9.7 deaths per 100,000 men and 6.9 per 100,000 women by 1987-91 (Ries et al., 1994). During this time, both underdiagnosis and overdiagnosis of pancreatic cancer was suspected; in the late 1940s, only 53 percent of cases were microscopically confirmed compared to 71 percent of cases by the mid-1970s (Devesa et al., 1987). In the United States, pancreatic cancer incidence is lower among Seventh Day Adventists and Mormons and higher among blacks and Jews (Mack, 1982; Gordis et al., 1980; MacMahon, 1982; Gordis and Gold, 1984). The median age at diagnosis is 70 years; it rarely occurs before age 40. Worldwide, pancreatic cancer occurs slightly more frequently in males than in females and in urban areas more than in rural regions. The highest incidence rates in the world were observed among blacks in the United States and New Zealand Maoris; the lowest rates were reported for India and Thailand (Parkin et al., 1992).

Little is known about the etiology of pancreatic cancer, but studies of ethnic and religious groups suggest that environmental factors play a dominant role. Cigarette smoking is the only established risk factor, with a two-fold risk for smokers relative to nonsmokers. In analytic studies, associations between pancreatic cancer and consumption of alcohol, coffee and tea, and previous medical conditions such as diabetes mellitus, pancreatitis, and allergies have been inconsistent (Velema et al., 1986; Falk et al., 1988; Mack et al., 1986; Mills et al., 1988). Excess pancreatic

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Pancreas

cancer deaths have been observed in some occupational cohorts exposed to chemicals or petroleum, including manufacturers of photographic film (Hearne et al., 1987), chemists (Li et al., 1969; Hoar and Pell, 1981), leather tanners (Constantini et al., 1989), and auto mechanics (Hansen, 1989), but case-control studies have not consistently confirmed these associations (Mack et al., 1985; Falk et al., 1990).

Ecologic studies correlate high pancreatic cancer rates with dietary fat (Maruchi et al., 1977), and recent analytical studies show high-fat foods such as meats and butter are associated with increased pancreatic cancer risk (Gold et al., 1985; Mack et al., 1986; Falk et al., 1988; Norell et al., 1986; Olsen et al., 1989; Farrow and Davis, 1990), while diets with high fruit and vegetable intake are associated with a reduced risk (Falk et al., 1988; Olsen et al., 1989; Norell et al., 1986; Gold et al., 1985; Bueno De Mesquita et al., 1991; Mack et al., 1986). High levels of dietary protease inhibitors found in beans, lentils, and peas have been associated with low rates of pancreatic cancer in Seventh Day Adventists (Mills et al., 1988). However, the specific dietary determinants of pancreatic cancer, if any, have not been identified.

REFERENCES

- Bueno De Mesquita HB, Maisonneuve P, Runia S, et al.: Intake of foods and nutrients and cancer of the exocrine pancreas: A population-based case-control study in the Netherlands. *Int J Cancer* 48:540-549, 1991.
- Constantini AS, Paci E, Miligi L, et al.: Cancer mortality among workers in the Tuscan tanning industry. *Br J Ind Med* 46:384-388, 1989.
- Devesa SS, Silverman DT, Young JL, Jr, et al.: Cancer incidence and mortality trends among whites in the United States, 1947-84. *J Natl Cancer Inst* 79:701-770, 1987.
- Falk RT, Pickle LW, Fontham ET, et al.: Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol* 128:324-336, 1988.
- Falk RT, Pickle LW, Fontham ET, et al.: Occupation and pancreatic cancer risk in Louisiana. *Am J Ind Med* 18:565-576, 1990.
- Farrow DC and Davis S: Diet and the risk of pancreatic cancer in men. *Am J Epidemiol* 132:423-31, 1990.
- Gold EB, Gordis L, Diener MD, et al.: Diet and other risk factors for cancer of the pancreas. *Cancer* 55:160-167, 1985.
- Gordis L: Epidemiology of pancreatic cancer. In *Reviews in Cancer Epidemiology*, vol 1 (Lilienfeld AM, ed.). New York: Elsevier, 1980, 84-117.
- Gordis L and Gold EB: Epidemiology of pancreatic cancer. *World J Surg* 8:808-821, 1984.
- Hansen ES: Mortality of auto mechanics. A ten-year follow-up. *Scand J Work Environ Health* 15:43-46, 1989.
- Hearne FT, Grose F, Pifer JW, et al.: Methylene chloride mortality study: Dose-response characterization and animal model comparison. *J Occup Med* 29:217-228, 1987.
- Hoar SK and Pell SA: A retrospective cohort study of mortality and cancer incidence among chemists. *J Occup Med* 23:485-494, 1981.
- Li FP, Fraumeni JF Jr, Mantel N, et al.: Cancer mortality among chemists. *J Natl Cancer Inst* 43:1159-1164, 1969.
- Mack TM: Pancreas. In *Cancer Epidemiology and Prevention* (Schottenfeld D, Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders, 1982.
- Mack TM, Peters JM, Yu MC, et al.: Pancreas cancer is unrelated to the workplace in Los Angeles. *Am J Ind Med* 7:253-266, 1985.
- Mack TM, Yu MC, Hanisch R, et al.: Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* 76:49-60, 1986.
- MacMahon B: Risk factors for cancer of the pancreas. *Cancer* 50:2676-2680, 1982.
- Maruchi N, Aoki S, Tsude K, et al.: Relation of food consumption to cancer mortality in Japan with special reference to international figures. 68:1-13, 1977.
- Mills PK, Beeson WL, Abbey DE, et al.: Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 61:2578-2585, 1988.
- Norell SE, Ahlbom A and Erwald R: Diet and pancreatic cancer: a case-control study. *Am J Epidemiol* 121:894-902, 1986.
- Olsen GW, Mandel JS, Gibson RW, et al.: A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health* 79:1016-1019, 1989.
- Parkin DM, Muir CS, Whelan S, et al.: *Cancer Incidence in Five Continents*, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*. National Cancer Institute, NIH Publ. No. 91-2789. Bethesda, MD, 1991.
- Veelma JP, Walker AM and Gold EB: Alcohol and pancreatic cancer: Insufficient epidemiologic evidence for a causal relationship. *Epidemiol Rev* 8:28-41, 1986.

Prostate

Richard B. Hayes,
D.D.S., Ph.D.*

The prostate gland, located at the base of the penis, surrounds the urethra and produces seminal fluid. Cancer of the prostate is one of the most common cancers among American men, with an incidence rate exceeding that for lung cancer. It is primarily a disease of the elderly: The median age at diagnosis is 72. While Europeans and American whites have high prostate cancer mortality rates, perhaps the highest reported mortality in the world for prostatic cancer is among American blacks. The lowest rates are found in Asians (Kurihara et al., 1989).

From 1973 to 1991, prostate cancer mortality in the United States increased at a rate of 1.0 percent per year among white males and 1.8 percent among blacks (Ries et al., 1994). However, among American blacks over the age of 65, the overall rate rose 45.2 percent for blacks—more than twice the rate for whites (22.4 percent).

Since the late 1940s, the rate of identification of prostate cancer cases has increased 67 percent or about 1.8 percent per year (Devesa et al., 1987). This dramatic increase is in part due to the greater frequency of operations for benign disease of the prostate, with the subsequent incidental finding of asymptomatic prostatic tumors, as well as the escalation in the use of new diagnostic technology including transrectal ultrasound guided needle biopsy, computer tomography, and serum testing for prostate-specific antigen (PSA). However, the steady increase in the mortality rates implies that the escalation in incidence is not solely attributable to incidental discovery and early detection, but to a real change in the risk of developing the disease (Miller et al., 1993).

While prostate cancer is uncommon among Japanese in Japan, Japanese in Hawaii have prostate cancer rates intermediate between those in Japan and the high incidence among Hawaiian whites. These results, and other studies that show migrant populations tending toward the prostate cancer risk pattern of their host country, strongly suggest that environmental factors contribute to the large differences in risk found between countries (Bosland, 1988). Many such factors are under investigation.

Prostate cancer rates are generally greater in countries where the population consumes more animal fat. Comparison of dietary habits of prostate cancer cases and controls has shown that cases overall consume more animal fats (Kolonel et al., 1988; Graham et al., 1983; Ross et al., 1987). No correlation has been noted with the consumption of fat from vegetable sources (Rose et al., 1986). Greater dietary intake of vitamin A has also been associated with an excess risk for prostate cancer in some studies (Kolonel et al., 1988; Graham et al., 1983), although high blood levels of retinol appear related to a decreased risk for this disease (Reichman, 1990).

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Prostate

The evidence for an important role of diet in prostate cancer development has increased over the last decade. Further studies supported by NCI are designed to specify these associations and to determine the contribution of dietary factors to ethnic differences in the United States in prostate cancer risk.

Other factors may also be involved in the development of this disease. Reports of greater sexual activity and frequency of venereal disease in prostate cancer cases than controls raises the possibility that some cases may be the result of a sexually transmitted agent (Ross et al., 1987) although no likely microorganism has been identified. A history of some benign prostatic disease, including prostatitis (Honda et al., 1985) and some types of hyperplasia (Kovi et al., 1988), may increase the risk of prostate cancer. Studies of occupational groups have shown farmers to be consistently at higher risks for prostate cancer (Blair et al., 1988), although it is unclear if this finding is the result of occupational factors or to concomitant lifestyle factors. Other studies weakly suggest associations with work in rubber manufacturing, iron and steel foundries, and some other manufacturing occupations (Bosland, 1988).

Although the mechanism of prostate cancer development is not understood, hormones, including the male androgenic hormone, testosterone, could play an important role. These hormones are essential in normal prostate development and function; their manipulation is important in prostate cancer treatment and in the development of prostate cancer in experimental animals. Diet (Howie and Schultz, 1985) and other factors (Dai et al., 1988) may influence hormone levels, and people at high risk for prostate cancer may have different hormone patterns than those at low risk (Ross et al., 1992). Recent studies (Barrett-Conner et al., 1990; Nomura et al., 1988) implicate various steroidal and related hormones, suggesting that the relationship of hormone status with prostatic cancer risk is likely complex.

REFERENCES

- Barrett-Conner E, Garland C, McPhillips JB, et al.: A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. *Cancer Res* 50:169-173, 1990.
- Blair A, Malke H, Cantor KP, et al.: Cancer among farmers: A review. *Scand J Work Environ Health* 11:397-407, 1985.
- Bosland M: The etiopathogenesis of prostate cancer with special reference to environmental factors. *Adv Cancer Res* 51:1-106, 1988.
- Dai WJ, Gutai JP, Kuller LH, et al., for the MRFIT Research Group: Cigarette smoking and serum sex hormones in men. *Am J Epidemiol* 128:796-805, 1988.
- Devesa SS, Silverman DT, Young JL, et al.: Cancer incidence and mortality trends among whites in the United States, 1947-84. *J Natl Cancer Inst* 79:701-770, 1987.
- Graham S, Haughey B, Marshall J, et al.: Diet in the epidemiology of carcinoma of the prostate gland. *J Natl Cancer Inst* 70:687-692, 1983.
- Honda GD, Bernstein L, Ross RK, et al.: Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 57:326-331, 1988.
- Howie BJ and Schultz TD: Dietary and hormonal interrelationships among vegetarian Seventh Day Adventists and nonvegetarian men. *Am J Clin Nutr* 42:127-134, 1985.
- Kolonel LN, Yoshizawa CN and Hankin JH: Diet and prostatic cancer: A case-control study in Hawaii. *Am J Epidemiol* 127:999-1012, 1988.
- Kovi J, Mostofi FK and Heshmat MY: Large acinar atypical hyperplasia and carcinoma of the prostate. *Cancer* 61:555-561, 1988.
- Kurihara M, Aoki K and Hisamichi S (eds.): *Cancer Mortality Statistics in the World 1950-1985*. Nagoya: University of Nagoya Press, 1989.
- Miller BA, Ries LAG, Hankey BF, et al. (eds.): *Cancer Statistics Review: 1973-1990*, National Cancer Institute, NIH Publ. No. 93-2789, 1993.
- Ries LAG, Miller BA, Hankey BF, et al.: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*, National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Nomura A, Heilbrun LK, Stemmermann GN, et al.: Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res* 48:3515-3517, 1988.
- Reichman ME, Hayes RB, Ziegler RG, et al.: Serum vitamin A and subsequent development of prostate cancer in the First Epidemiologic National Health and Nutrition Examination Survey I Followup Study. *Cancer Res* 50:2311-2315, 1990.
- Ross RK, Bernstein L, Lobo, RA, et al.: 5-alpha-reductase activity among Japanese and U.S. white and black males. *Lancet* 339:887-889, 1992.
- Ross RK, Shimizu H, Paganini-Hill A, et al.: Case-control studies of prostate cancer in blacks and whites in Southern California. *J Natl Cancer Inst* 78:869-874, 1987.
- Rose DP, Boyar AP and Wynder EL: International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. *Cancer* 58:2363-2371, 1986.

Skin (Nonmelanoma)

Joseph Scotto, M.S.*

Nonmelanoma skin cancer is the most common cancer among whites in the United States. Because most nonmelanoma skin cancer patients are treated in doctors' offices, population-based estimates of skin cancer incidence are fairly difficult to obtain. More than 600,000 new cases of nonmelanoma skin cancer may occur in the United States each year, and this number is rising (Glass and Hoover, 1989; NIH Consensus Development Conference, 1989). The fatality rate from non-melanoma skin cancer is less than 1 percent (Marks, 1988).

The incidence of nonmelanoma skin cancer varies directly with exposure to ultraviolet (UV) light from the sun and, indirectly, with the degree of skin pigmentation. Thus, nonmelanoma skin cancer is most common among fair-skinned whites who live in sunny locales. The highest rates in the past have been recorded among Caucasians in South Africa and Australia (Marks et al., 1989). Ireland, despite its rain and mist, has had a high incidence because of the susceptibility of persons of Celtic ancestry (Urbach, 1971).

Nonmelanoma skin cancer occurs less often in Hispanics and Orientals, and least often among blacks. In the United States, for example, a National Cancer Institute survey (Scotto, 1983) showed that the age-adjusted incidence rate was only 3.4 per 100,000 among blacks, or about 80 times less than the rate observed among whites.

Most nonmelanoma skin cancers are of two types—squamous cell carcinoma and basal cell carcinoma. The basal cell type is more common, but the squamous cell type is more invasive, and may account for about three-fourths of all deaths from nonmelanoma skin cancer (Dunn et al., 1965).

Several studies have shown that basal cell skin cancer occurs about one and one-half to two times more often in white men than in white women, and squamous cell skin cancer occurs two to three times more often in men. Both types occur most often on the face, head and neck (about 80 percent for both types combined). Women have higher rates than men for both types of cancers on the legs (Scotto, 1982), consistent with their greater sun exposure at this anatomical site. White men have more squamous cell carcinoma of the lip, in line with their risks from tobacco and outdoor work (Lindqvist, 1979).

Skin cancer incidence in the United States is positively correlated with annual dosages of surface solar ultraviolet radiation (UVB) received at each geographic location (Fears and Scotto, 1983). The direct relationship is most clearly seen with squamous cell carcinoma of the skin (Scotto and Fraumeni, 1982), and varies according to cell type. A 1 percent increase in UVB exposure may result in incidence increases of 4, 2, and 1 percent for squamous cell, basal cell, and malignant melanoma of the skin, respectively. This is consistent with the evidence that factors other than sunlight also contribute to the development of melanoma (Greene and Fraumeni, 1979).

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

Skin (Nonmelanoma)

There are other risk factors for nonmelanoma skin cancers. They were, for example, the first type of cancer related to ionizing radiation exposure, with reports as early as 1902 among radiation workers (Martin, 1970). Other studies have shown an excess risk associated with radiotherapy for a number of diseases (Matanoski, 1975). Excess risks have also been noted among radiologists and uranium miners (Sevcova, 1978).

Exposure to a number of chemicals may also induce skin cancer in animals, particularly squamous cell carcinoma. Epidemiologic studies substantiate their associated risk in humans. Polycyclic aromatic hydrocarbons induce cancers in animals and are found in coal tars, pitch, asphalt, soot, creosote, and lubricating and cutting oils (Kipling, 1976). Skin and other forms of cancer have been found in various worker groups exposed to these substances. Though Orientals rarely develop sun-induced skin cancer, arsenic exposure (e.g., from artesian well water) may result in excess risk for skin cancer (EPA, 1988).

Studies have shown an excess risk of skin cancer among psoriasis patients treated with crude tar ointments and UVA, i.e., ultraviolet wavelengths of 330 to 400 nm, (Stern, 1980), and there has been increased concern about the possible hazards of other photosensitizers found in tanning aids, cosmetics, and medicines (NIH Consensus Development Conference, 1989).

Squamous cell skin cancer has also been observed as a complication of tropical ulcers, burns, scars, and chronic infections and wounds (Malik et al., 1974), chiefly among dark-skinned populations in Africa and Asia, but recent studies of black Americans have indicated that burn scars or chronic infections may predispose them to skin cancer also (Fleming, 1975). Actinic keratoses—brownish, hardened areas on skin exposed to excess sunlight—are considered precursor lesions for squamous cell skin cancer (Marks, 1988). Individuals with several rare hereditary diseases, including multiple basal cell carcinoma syndrome, xeroderma pigmentosum, and albinism, are also at heightened risk of developing skin cancer (Kraemer, 1984).

Avoiding overexposure to sunlight is the best way to prevent nonmelanoma skin cancer. In addition to natural sunlight, it is also important to avoid unnecessary X-rays and ultraviolet light exposure from artificial sources such as sunlamps and tanning booths.

REFERENCES

- Dunn JE Jr, Levin EA, Linden G, et al.: Skin cancer as a cause of death. *Calif Med* 102:361-3, 1965.
- EPA Risk Assessment Forum: Special report on ingested inorganic arsenic—Skin Cancer; Nutritional essentiality. U.S. Environmental Protection Agency, EPA-625/3-87-013, Washington, DC, 1988.
- Fears TR and Scotto J: Estimating increases in skin cancer morbidity due to increases in ultraviolet radiation exposure. *Cancer Invest* 1(2):119-26, 1983.
- Fleming DD, Barnawell JR, Burlison PE, et al.: Skin cancer in black patients. *Cancer* 35:600-5, 1975.
- Glass AG and Hoover RN: The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 262 (15):2097-100, October 20, 1989.
- Greene MH and Fraumeni JF Jr: The hereditary variant of malignant melanoma. In *Human Malignant Melanoma* (Clark WH, Goldman LJ, Mastrangelo MJ, eds.). New York: Grune and Stratton, 1979.
- Kipling MD and Waldron HA: Polycyclic aromatic hydrocarbons in mineral oil, tar, and pitch, excluding petroleum pitch. *Prev Med* 5:262-78, 1976.
- Kraemer KH, Lee MM and Scotto J: DNA repair protects against cutaneous and internal neoplasia: Evidence from xeroderma pigmentosum. *Carcinogenesis* 5:511-1, 1984.
- Lindqvist C: Risk factors in lip cancer: A questionnaire survey. *Am J Epidemiol* 109:521-30, 1979.
- Malik MOA, Hidayatalla A, Daoud EI, et al.: Superficial cancer in the Sudan—A study of 1225 primary malignant superficial tumours. *Br J Cancer* 30:355-64, 1974.
- Marks R, Rennie G and Selwood TS: Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1(8589):795-7, April 9, 1988.
- Marks R, Jolley D, Dorevitch AP, et al.: The incidence of non-melanocytic skin cancers in an Australian population: Results of a five-year prospective study. *Med J Aust* 150(9):175-8, 1989.
- Martin H, Strong E and Spiro RH: Radiation-induced skin cancer of the head and neck. *Cancer* 25:61-71, 1970.
- Matanoski GM, Selser R, Sartwell PE, et al.: The current mortality rates of radiologists and other physician specialists: Specific causes of death. *Am J Epidemiol* 101:199-210, 1975.
- NHI Consensus Development Conference Statement: Sunlight, Ultraviolet Radiation and the Skin, vol 7, no 8, May 8-10, 1989.
- Scotto J, Fears TR and Fraumeni JF Jr: Incidence of Nonmelanoma Skin Cancer in the United States. NCI NHI Publ. No. 83-2133, April 1983.
- Scotto J and Fraumeni JF Jr: Skin (other than melanoma). In *Cancer Epidemiology and Prevention* (Schottenfeld D, and Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders, 1982.
- Sevcova M, Sevc J and Thomas J: Alpha irradiation of the skin and the possibility of late effects. *Health Physics* 35:803-6, 1978.
- Stern RS, Zierler S and Parish JA: Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1:732-5, 1980.
- Urbach F: Geographic distribution of skin cancer. *J Surg Oncol* 3:219-34, 1971.

Stomach

Robert Kneller, M.D.*

In the 1930s, stomach cancer was the leading cause of death among U.S. men and the third leading cause among U.S. women after cancers of the uterus and breast (Boring et al., 1991). Since then, the death rates have dropped dramatically—approximately 80 percent among men and 90 percent among women (American Cancer Society, 1991). Today, stomach cancer ranks eighth as a cause of cancer death, and U.S. death rates due to stomach cancer are among the lowest in the world (Boring et al., 1994).

Despite the decrease, stomach cancer is still a major problem. About 24,000 new cases were expected in the United States in 1994 (Boring et al., 1994), and only 18 percent of these patients will live five years after diagnosis (Ries et al., 1994). This represents one of the poorer survival rates for any type of cancer in the U.S., and may be due partly to the fact that the disease usually is not detected until it has spread beyond the stomach (MacDonald et al., 1989). In addition, cancer of the upper portion of the stomach, along with adenocarcinomas of the lower esophagus, recently have become more common, particularly among white men (Blot et al., 1991).

Stomach cancer is the leading cause of cancer death in many countries, including Japan and China (Kurihara et al., 1989). Along with lung cancer, it is a leading cause of cancer death worldwide (Parkin et al., 1988). The highest international rates were noted among the Japanese, with world standardized rates for males of more than 70/100,000. Comparable rates for U.S. males were only 10 and 13 percent of the highest worldwide rate for blacks and whites, respectively (Parkin et al., 1992). In most areas of the world, stomach cancer occurs about twice as often among males as females. When persons from regions such as Japan and Eastern Europe migrate to the United States, their stomach cancer rates decrease over successive generations, though lifetime risks approximate most closely those of the country of early childhood (Nomura, 1982).

Migrant studies and the marked decrease in death rates in the United States and many other countries suggest that environmental factors play a dominant role. The advent of widespread refrigeration that began in the United States in the 1930s may be partly responsible for the reduced rates (Nomura, 1982). Refrigeration reduced the need for other methods of food preservation and allowed access to fresh fruits and vegetables year round. Surveys have shown that stomach cancer patients eat fewer fresh fruits and vegetables than persons without stomach cancer (Nomura, 1982; Buiatti et al., 1989). Several studies suggest that consumption of allium vegetables (e.g., onions and garlic) and foods rich in carotenes or vitamins C or E are associated with decreased risk of stomach cancer (You et al., 1989; Buiatti, 1989, 1990), while intake of salted, pickled, or smoked foods may increase risk (Nomura, 1982; Buiatti, 1989).

* From the Fogarty International Center, National Institutes of Health, Bethesda, Maryland

Stomach

Studies in many countries have shown that low socioeconomic status is associated with stomach cancer (Nomura, 1982). A recent study suggests that crowding during early childhood may be related to higher risk among lower socioeconomic classes (Barker et al., 1990). An increased risk of stomach cancer among cigarette smokers has also been detected in several studies (McLaughlin et al., 1990; Kneller, 1991).

Stomach cancer is often preceded by a series of changes in the lining of the stomach that occurs over many years. These changes begin with inflammation of the stomach lining (gastritis), then progress to loss of the glandular cells that make up much of the stomach lining (chronic atrophic gastritis), to replacement of these cells by cells resembling those found in the lining of the intestines, to abnormal changes within these intestinal-like cells, and, finally, to the uncontrolled growth of these abnormal cells, signifying cancer (Correa, 1988). N-nitroso compounds (NNCs) may play an important role in inducing these changes (Correa, 1988). While tobacco contains carcinogenic NNCs (Bartsch, 1984), and there are other environmental sources for preformed NNCs (National Academy of Sciences, 1981), the most harmful NNCs are believed to be formed inside the stomach when nitrite combines with nitrogen-containing compounds in foods, prescription drugs, or tobacco smoke (Mirvish, 1983; Bartsch, 1984, 1989). Nitrites are found in a variety of foods, especially pickled or cured foods (National Academy of Sciences, 1981). Nitrites can also be formed from nitrate, which is common in many foods and water supplies (Mirvish, 1983). Vitamins C and E block the formation of NNCs (Mirvish, 1983; Bartsch, 1989), which may explain the protective associations noted above.

Other factors may be involved at the cellular level. It has been proposed that infection with *Helicobacter pylori*, now believed to be a common cause of gastritis and peptic ulcers (Peterson, 1991), may play a role in the initiation of precancerous stomach changes (Correa, 1991). Risk of stomach cancer is increased in patients with pernicious anemia. Pernicious anemia, which is believed to be an immune disorder, results in many of the changes in the stomach lining seen with chronic atrophic gastritis (MacDonald et al., 1989). Studies of atomic bomb survivors and patients treated with X-rays for a spinal disorder indicate that radiation may increase risk (Nomura, 1982).

Evidence for a genetic component comes from reports that persons with blood type A, an inherited trait, may be at increased risk for both stomach cancer and pernicious anemia (Nomura, 1982). Family studies suggest a possible genetic susceptibility (Nomura, 1982; Correa, 1988), though it is difficult to distinguish between genetic and environmental influences among persons who have shared the same environment.

For the general population, a diet rich in fresh fruits and vegetables may reduce risk, as might limiting tobacco use and consumption of pickled, smoked, or heavily salted foods.

REFERENCES

- Barker DJP, Coggon D, Osmond C, et al.: Poor housing in childhood and high rates of stomach cancer in England and Wales. *Br J Cancer* 6:575-8, 1990.
- Bartsch H and Montesano R: Relevance of nitrosamines to human cancer. *Carcinogenesis* 5:1381-93, 1984.
- Bartsch H, Ohshima H, Pignatelli B, et al.: Human exposure to endogenous N-nitroso compounds: Quantitative estimates in subjects at high risk for cancer of the oral cavity, oesophagus, stomach and urinary bladder. *Cancer Surveys* 8:335-62, 1989.
- Blot WJ, Devesa SS, Kneller RW, et al.: Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 265:1287-1289, 1991.
- Boring CC, Squires TS and Tong T: Cancer statistics, 1991. *CA Cancer J Clin* 41:19-36, 1991.
- Buiatti E, Palli D, Decarli A, et al.: A case-control study of gastric cancer and diet in Italy. *Int J Cancer* 44:611-6, 1989.
- Buiatti E, Palli D, Decarli A, et al.: A case-control study of gastric cancer and diet in Italy: II. Association with nutrients. *Int J Cancer* 45:896-901, 1990.
- Correa P: A human model of gastric carcinogenesis. *Cancer Res* 48:3554-60, 1988.
- Correa P: Is gastric carcinoma an infectious disease? (letter) *N Engl J Med* 325:1170-1171, 1991.
- Kneller RW, McLaughlin JK, Bjelke E, et al.: A cohort study of stomach cancer in a high-risk American population. *Cancer* 68:672-678, 1991.
- Kurihara M, Aoki K and Hisamichi S (eds.): Cancer Mortality Statistics in the World 1950-85, Nagoya: University of Nagoya Press, 1989.
- McLaughlin JK, Hrubec Z, Blot WJ, et al.: Stomach cancer and cigarette smoking among U.S. veterans, 1954-1980. *Cancer Res* 50:3804, 1990.
- Mirvish SF: The etiology of gastric cancer: Intragastric nitrosamide formation and other theories. *J Natl Cancer Inst* 71:631-647, 1983.
- National Academy of Sciences: The Health Effects of Nitrate, Nitrite and N-Nitroso Compounds, Chapter 12. Washington, DC: National Academy Press, 1981.
- Nomura A: Stomach. In *Cancer Epidemiology and Prevention* (Schottenfeld D and Fraumeni JF Jr, eds.). Philadelphia: W.B. Saunders, 1982.
- Parkin DM, Laara E and Muir CS: Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int J Cancer* 41:184-97, 1988.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Peterson WL: Helicobacter pylori and peptic ulcer disease. *N Engl J Med* 324:1043-8, 1991.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs. National Cancer Institute. NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- You WC, Blot WJ, Chang YS, et al.: Allium vegetables and reduced risk of stomach cancer. *J Natl Cancer Inst* 81:162-4, 1989.

Testis

Linda Morris Brown, M.P.H.*

The testes are the paired male reproductive glands that produce the hormone testosterone and, after sexual maturity, spermatozoa (sperm). The testes form in the abdominal cavity early in fetal development and usually descend into the scrotum before birth. Almost all testicular cancers are germ cell tumors. There are two major histological groupings of testicular cancer: seminoma and nonseminoma. Seminomas are more common in men 35 and older, while nonseminomas are more common in younger men 15–24 (Brown et al., 1986a).

Testicular cancer is rare in the United States, accounting for only 1 percent of cancers in males. It is, however, the most common malignancy among white males aged 20 to 34 and the second most common among white males aged 15 to 19 and 35 to 39. The incidence rate for white males (5.1 per 100,000) is over six times that for black males (0.8 per 100,000) (Ries et al., 1994). In the United States, the incidence rates of testicular cancer among Hispanics, Native Americans, and Asians are less than those for whites, but greater than those for blacks (Muir et al., 1987). Men in Scandinavian countries have the highest incidence of testicular cancer in the world—a rate 45 percent greater than that for white men in the United States (Parkin et al., 1992).

Mortality from testicular cancer is low in both white (0.3 per 100,000) and black (0.1 per 100,000) U.S. males (Ries et al., 1994). Because of advances in treatment, survival was 94 percent in 1983–90, up from 79 percent in 1974–76.

The incidence of testicular cancer has doubled in the past two decades, with the most striking increases occurring among young men 15–44. Undescended testis, inguinal hernia, testicular trauma, mumps orchitis, elevated testicular temperature, vasectomy, electromagnetic fields (EMF), and hormonal, prenatal, and occupational factors have been implicated in the development of testicular cancer in young adults.

Individuals with cryptorchidism or undescended testis are at an increased risk for developing testicular cancer, with approximately 10 percent of testicular cancer patients reporting a history of this condition. Risks of testicular cancer associated with undescended testes have ranged from 2.5 to 17.1 (Brown et al., 1987), with the excess risk in cryptorchid men decreasing with increasingly early age at correction (Pottern et al., 1985; Strader et al., 1988a).

Inconsistent findings regarding the degree and significance of the risk of testicular cancer associated with inguinal (groin) hernia have been reported (Coldman et al., 1982; Pottern et al., 1985; Swerdlow et al., 1987a). Significantly elevated risks have been suggested for other antecedent conditions including hydrocele, atrophic testis, and supernumerary nipples (polythelia) (Goedert et al., 1984; Swerdlow et al., 1987a; Haughey et al., 1989; Brown et al., 1987). Also, a higher rate of

* From the Biostatistics Branch,
Division of Cancer Etiology, National
Cancer Institute, Bethesda, Maryland

cryptorchidism, inguinal hernia, and hydrocele was reported in families prone to testicular cancer, suggesting a relationship between urogenital maldevelopment and predisposition to testicular cancer (Tollerud et al., 1985).

An association between testicular trauma and testicular cancer has been suggested (Brown et al., 1987; Coldman et al., 1982); however, another study (Swerdlow et al., 1988a) found no association with traumas commonly encountered in everyday life. Although a recent study in upstate New York (Haughey et al., 1989) reported elevated risks for men who preferred baths to showers and who reported having a disease associated with a high fever, three other case-control studies found no excess risk associated with elevation of testicular temperature by external means (Brown et al., 1987; Swerdlow et al., 1988a; Karagas et al., 1989). Two suggested risk factors, vasectomy and EMF exposure from the use of electric blankets, have not been found to be significant risk factors for testicular cancer (Brown et al., 1987; Strader et al., 1988a; Verreault et al., 1990).

Maternal factors including nausea of pregnancy severe enough to require treatment, unusual bleeding or spotting during pregnancy, as well as low birth weight and early birth order have been associated with excess risk of testicular cancer (Depue et al., 1983; Brown et al., 1986b; Swerdlow et al., 1987b; Gershman et al., 1988) and suggest that raised maternal levels of available estrogen early in pregnancy may be related to development of testicular cancer in the son. Although in utero DES exposure has been linked to vaginal cancer in daughters and to testicular abnormalities in sons of women who took it to prevent miscarriages (DES Task Force, 1981), prenatal DES exposure has not been linked to testicular cancer (Brown et al., 1986b; Moss et al., 1986; Gershman et al., 1988).

An association between employment in professional occupations and the risk of testicular cancer has been reported in several case-control studies (Graham et al., 1977; Ross et al., 1979; Swerdlow et al., 1988b). Farming has been associated with excess risk of testicular cancer in some studies (Mills et al., 1984; Wiklund et al., 1986), but not in others (Brown and Pottern, 1984; Jensen et al., 1984; Sewell et al., 1986). A recent case-control study found a significant increase in risk for exposure to fertilizers (Haughey et al., 1989).

The dramatic increase in testicular cancer incidence over time for young men suggest that an environmental factor, with a similar variation over time, might be responsible. Given the magnitude of this increase, one would expect that this factor should have been identified by analytical epidemiological studies. However, to date the factors responsible for these dramatic increases remain elusive. The increases do not appear to be related to improved diagnostic practices nor to any of the risk factors identified to date in case-control studies.

REFERENCES

- Brown LM, Pottern LM: Testicular cancer and farming. *Lancet* 1:1356, 1984.
- Brown LM, Pottern LM, Hoover RN, et al.: Testicular cancer in the United States: Trends in incidence and mortality. *Int J Cancer* 15:164-170, 1986a.
- Brown LM, Pottern LM and Hoover RN: Prenatal and perinatal risk factors for testicular cancer. *Cancer Res* 46:1812-1816, 1986b.
- Brown LM, Pottern LM and Hoover RN: Testicular cancer in young men: The search for causes of the epidemic increase in the United States. *J Epidemiol Commun Health* 41:349-354, 1987.
- Coldman AJ, Elwood JM and Gallagher RP: Sports activities and risk of testicular cancer. *Br J Cancer* 46:749-756, 1982.
- Depue RH, Pike MC and Henderson BE: Estrogen exposure during gestation and risk for testicular cancer. *J Natl Cancer Inst* 71:1151-1155, 1983.
- DES Task Force Summary Report: DHHS Publ. No. (NIH) 81-1688, Bethesda, MD, 1981.
- Goedert JJ, McKeen EA, Javadpour N, et al.: Polythelia and testicular cancer. *Ann Intern Med* 101:646-647, 1984.
- Gershman ST and Stolley PD: A case-control study of testicular cancer using Connecticut Tumor Registry data. *Int J Epidemiol* 17:738-742, 1988.
- Graham S, Gibson R, West D, et al.: Epidemiology of cancer of the testis in upstate New York. *J Natl Cancer Inst* 58:1255-1261, 1977.
- Haughey BP, Graham S, Brasure J, et al.: The epidemiology of testicular cancer in upstate New York. *Am J Epidemiol* 130:25-36, 1989.
- Jensen OM, Olsen JH and Osterlind A: Testis cancer among farmers in Denmark. *Lancet* 1:794, 1984.
- Karagas MR, Weiss NS, Strader CH, et al.: Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. *Am J Epidemiol* 129:1104-1109, 1989.
- Mills PK, Newell GR and Johnson DE: Testicular cancer associated with employment in agriculture and oil and natural gas extraction. *Lancet* 1:207-210, 1984.
- Moss AR, Osmond D, Bacchetti P, et al: Hormonal risk factors in testicular cancer—a case-control study. *Am J Epidemiol* 124:39-52, 1986.
- Parkin DM, Muir CS, Whelan S, et al.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120, World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Pottern LM, Brown LM, Hoover RN, et al.: Testicular cancer risk among young men: Role of cryptorchidism and inguinal hernia. *J Natl Cancer Inst* 74:377-381, 1985.
- Ries LAG, Miller BA, Hankey BE, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs. National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Ross RK, McCartis RW, Henderson BE, et al.: Descriptive epidemiology of testicular and prostatic cancer in Los Angeles. *Br J Cancer* 39:284-292, 1979.
- Sewell CM, Casile SP, Hull HF, et al.: Testicular cancer and employment in agriculture and oil and natural gas extraction. *Lancet* 1:553, 1986.
- Strader CH, Weiss NS, Daling JR, et al.: Cryptorchism, orchiopexy, and the risk of testicular cancer. *Am J Epidemiol* 127:1013-1018, 1988a.
- Strader CH, Weiss NS and Daling JR: Vasectomy and the incidence of testicular cancer. *Am J Epidemiol* 128:56-63, 1988b.
- Swerdlow AJ, Huttly SRA and Smith PG: Testicular cancer and antecedent diseases. *Br J Cancer* 55:97-103, 1987a.
- Swerdlow AJ, Huttly SRA and Smith PG: Prenatal and familial associations of testicular cancer. *Br J Cancer* 55:571-577, 1987b.
- Swerdlow AJ, Huttly SR and Smith PG: Is the incidence of testis cancer related to trauma or temperature? *Br J Urol* 61:518-521, 1988a.
- Swerdlow AJ and Skeet RG: Occupational associations of testicular cancer in southeast England. *Br J Ind Med* 45:225-230, 1988b.
- Tollerud DJ, Blattner WA, Fraser MC, et al.: Familial testicular cancer and urogenital developmental anomalies. *Cancer* 55:1849-1851, 1985.
- Verreault R, Weiss NS, Hollenbach KA, et al.: Use of electric blankets and risk of testicular cancer. *Am J Epidemiol* 131:759-762, 1990.
- Wiklund K, Dich J and Holm LE: Testicular cancer among agricultural workers and licensed pesticide applicators in Sweden. *Scand J Work Environ Health* 12:630-631, 1986.

Urinary Bladder

Debra T. Silverman, Sc.D.*

Bladder cancer is the fifth most common cancer in the United States, where it is chiefly a disease of white men over age 65. For 1994, 51,200 new cases and 10,000 deaths were estimated (Boring et al., 1994). The incidence of 32.3 cases per 100,000 population among white men is more than twice that found in non-white men. There is little racial difference in incidence among women, who develop bladder cancer about a fourth as often as men.

From 1973 to 1991, the overall incidence of bladder cancer increased 10 percent (Ries et al., 1994). There was, however, a 28 percent increase for black men and a 34 percent increase for black women. From the early 1960s, 5-year relative survival among patients with bladder cancer increased more than 50 percent to a level of 80 percent for whites and 60 percent for blacks.

Internationally, the incidence of bladder cancer varies about 10-fold (Parkin et al., 1992). The disease occurs most often in Western Europe and North America and least often in Eastern Europe and several areas of Asia (Silverman et al., in press).

The most important known risk factor for bladder cancer is cigarette smoking; cigarette smokers develop bladder cancer two to three times more often than nonsmokers (Silverman et al., in press). Risk increases with amount smoked (number of packs per day), with moderate to heavy smokers experiencing two to five times the risk of nonsmokers. Quitting smoking is associated with a 30 to 60 percent decrease in risk. Smoking is estimated to be responsible for about 48 percent of the bladder cancers among men and 32 percent among women in the United States.

As early as 1895, workers in the dyestuffs industry showed a high risk of bladder cancer that was later associated with exposure to certain aromatic amines, a class of compounds used to make dyes (Silverman et al., 1992a). Two of these chemicals, benzidine and 2-naphthylamine, are now known to be potent bladder carcinogens in humans (Case, 1954). Workers in the rubber and leather industries also have an increased risk of developing bladder cancer. Occupations in which workers are suspected of having an elevated bladder cancer risk include painter, driver of trucks and other motor vehicles, aluminum worker, machinist, chemical worker, printer, metal worker, hairdresser, and textile worker (Silverman et al., in press).

The possible risk of bladder cancer associated with widely used artificial sweeteners received much attention when the Food and Drug Administration removed cyclamates from the market in 1969. It was later reported that the sweetener saccharin caused bladder cancer in male laboratory rats when the animals were exposed to

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Urinary Bladder

the chemicals before birth (Silverman et al., 1992a). But epidemiological studies show that, overall, people who use artificial sweeteners do not appear to have a higher incidence of bladder cancer than nonusers (Morrison and Buring, 1980; Hoover et al. 1980).

Although some studies have indicated a possible link between bladder cancer and coffee drinking, other studies have found little or no increase in bladder cancer incidence among coffee drinkers compared with those who do not drink coffee (Silverman et al., in press). The inconsistency of these observations suggests that, if coffee drinking is associated with bladder cancer, the association is a weak one.

Other factors that may contribute to the development of bladder cancer include bladder infection with the parasitic fluke *Schistosoma haematobium*, treatment with the anticancer drugs chlornaphazine or cyclophosphamide, long-term use of pain killers containing the drug phenacetin, urinary tract infections and stasis, dietary factors, tobacco products other than cigarettes (e.g., pipes and cigars), and genetic susceptibility (Silverman et al., in press).

REFERENCES

- Boring CC, Squires TS and Tong T. Cancer Statistics, 1994. *CA Cancer J Clin* 1994; 44:7-26, 1994.
- Case RAM, Hosker ME, McDonald DB, et al.: Tumours of the urinary bladder in the workmen engaged in the manufacture and use of certain dyestuff intermediates in the British Chemical Industry. *Br J Ind Med* 11:75-104, 1954.
- Hoover RN, Strasser PH, Child M, et al.: Artificial sweeteners and human bladder cancer. *Lancet* 1:837-840, 1980.
- Morrison AS and Buring JE: Artificial sweeteners and cancer of the lower urinary tract. *N Engl J Med* 302:537-541, 1980.
- Parkin DM, Muir CS, Whelan S, et al., eds.: Cancer Incidence in Five Continents, vol VI. IARC Scientific Publication No. 120. World Health Organization, International Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Pub. No. 94-2789, Bethesda, MD, 1994.
- Silverberg E, Boring CC and Squires TS: Cancer statistics, 1990. *CA Cancer J Clin* 40:9-26, 1990.
- Silverman DT, Hartge P, Morrison AS, et al.: Epidemiology of bladder cancer. *Hematol Oncol* 6:1-30, 1992a.
- Silverman DT, Morrison AS and Devesa SS: Bladder cancer. In Cancer Epidemiology and Prevention (Schottenfeld D, Fraumeni JF Jr, eds.), in press.

Uterine Cervix

Louise A. Brinton, Ph.D.*

The uterine cervix is the small cylindrical neck that leads from the uterus, or womb, into the vagina. A knob of the cervix protrudes into the vagina and can be visualized on physical examination. Cell samples are taken from this part of the cervix for the Pap smear test, which is used to detect cancer cells or changes in cell structure that may lead to cancer. The most commonly detected changes are dysplasias, which are thought to be precursor conditions for carcinoma in situ (CIS) and invasive cancer of the cervix. However, many dysplasias regress over time, and the factors that lead to progression are unclear.

In CIS, an outer layer of normal cells has been replaced by cancer cells. It is about 95 percent treatable and curable. In invasive cancer of the cervix, the cancer cells have invaded the underlying tissue of the cervix. CIS occurs most often among women 25 to 31 years of age, while invasive cervical cancer most often is diagnosed in women over the age of 50.

Both incidence and mortality for invasive cancer of the uterine cervix have declined steadily in this country over the past three decades (Devesa et al., 1989). Nevertheless, black women continue to experience incidence rates that are nearly two times higher than those in whites. Racial differences are also evident in survival statistics; blacks have a 56 percent five-year relative survival rate compared with 70 percent for whites (Ries et al., 1991). The racial differences may be due, in part, to the association of cervical cancer with the sexual and other behavioral characteristics of low socioeconomic status.

High rates for cervical cancer are found in the American South, particularly in Appalachia. The U.S. incidence rates are generally low, however, compared to other parts of the world, such as India and South America, which have world standardized rates over 40 per 100,000. The comparable world standardized rate for U.S. black women is 12 and, for white women, 7 per 100,000 (Parkin et al., 1992).

Sexual behavior has been identified as the major risk factor for both CIS and invasive cervical cancer (Brinton and Fraumeni, 1986). Risk of both conditions is increased in women reporting either early age at first intercourse or numerous lifetime sexual partners. Early onset of sexual activity is thought to be associated with high risk because, during puberty, cervical tissue undergoes a variety of changes that may make the area more vulnerable. Because early intercourse is usually correlated with the eventual number of sexual partners, several studies have attempted to disentangle the two factors. They have found that the greater the number of sexual partners, the greater the risk of sexually transmitted disease; consequently, much research has focused on the role of a variety of sexually transmitted agents. Further supporting sexually transmitted agents in the etiology of this disease are several studies which indicate that there may be an important "male factor" to this

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Uterine Cervix

disease; husbands of cervical cancer patients report considerably more sexual partners than husbands of unaffected women (Brinton et al., 1989b; Buckley et al., 1981). Despite early speculation regarding potential effects, more recent studies do not confirm a role for circumcision status of the male partner. Frequency of sexual intercourse with the same male partner also appears unrelated to risk.

Recently, intense interest has focused on the role of the human papillomaviruses (HPV), which cause genital warts in both men and women (Koutsky et al., 1988). Abundant laboratory and clinical data support a role for HPV in the etiology of cervical cancer, but it is unlikely that the virus is a necessary and sufficient cause (Schiffman et al., 1993). The role of possible cofactors, including the herpesviruses, hormonal and dietary factors, and smoking, is also being investigated.

In a number of studies, cigarette smoking has been found to increase the risk of cervical cancer, especially among long-term or high-intensity smokers (Winkelstein, 1990). Smoking constituents have been found in cervical mucus, but the biologic mechanisms underlying the smoking-cervical cancer relationship have not been identified.

Choice of contraceptive method also appears to affect the risk of cervical cancer. Barrier mechanisms lower the risks—probably by decreasing exposure to infectious agents. The reasons for the increased risk associated with oral contraceptives—especially in long-term use—may be more complex. Although there has been concern that the link may merely reflect the correlation of this method with more intensive sexual activity, a number of studies have shown that the excess risk persists after adjustment for a variety of socioeconomic and sexual factors (Brinton, 1991). The role of hormonal factors in the etiology of cervical cancer has been underscored by recent studies which identify multiple births as independent risk factors (Brinton et al., 1989a; Parazzini et al., 1989).

There is increasing evidence that nutritional factors may play a role in cervical disease. Several studies suggest that low intake of either vitamin C or beta carotene may be associated with elevations in risk (Brock et al., 1988; Slattery et al., 1990), although this has not always been found (Ziegler et al., 1990). Deficiency in folacin (one of the B complex vitamins) has also been proposed as a risk factor, especially among oral contraceptive users whose stores of this vitamin are depleted.

REFERENCES

- Brinton LA: Oral contraceptives and cervical neoplasia. *Contraception* 43:581-595, 1991.
- Brinton LA and Fraumeni JF Jr: Epidemiology of uterine cervical cancer. *J Chron Dis* 39:1051-1065, 1986.
- Brinton LA, Reeves WC, Brenes MM, et al.: Parity as a risk factor for cervical cancer. *Am J Epidemiol* 130:486-496, 1989a.
- Brinton LA, Reeves WC, Brenes MM, et al.: The male factor in the aetiology of cervical cancer among sexually monogamous women. *Int J Cancer* 41:199-203, 1989b.
- Brock KE, Berry G, Mock PA, et al.: Nutrients in diet and plasma and risk of in situ cervical cancer. *J Natl Cancer Inst* 80:580-585, 1988.
- Buckley JD, Doll R, Harris RWC, et al.: Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 2:1010-1015, 1981.
- Devesa SS, Young JL Jr, Brinton LA, et al.: Recent trends in cervix uteri cancer. *Cancer* 64:2184-2190, 1989.
- Koutsky LA, Galloway DA and Holmes KK: Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 10:122-163, 1988.
- Parazzini F, La Vecchia C, Negri E, et al.: Reproductive factors and the risk of invasive and intraepithelial cervical neoplasia. *Br J Cancer* 59:805-809, 1989.
- Parkin DM, Muir CS, Whelan S, et al., eds.: *Cancer Incidence in Five Continents*, vol VI. IARC Publication No. 120, World Health Organization, IARC Scientific Agency for Research on Cancer, Lyon, 1992.
- Ries LAG, Miller BA, Hankey BF, et al.: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*. National Cancer Institute, NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Schillman MH, Bauer HM, Hoover RN, et al.: Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 85:958-964, 1993.
- Slattery ML, Abbott TM, Overall JC Jr, et al.: Dietary vitamins A, C, and E and selenium as risk factors for cervical cancer. *Epidemiology* 1:8-15, 1990.
- Winkelstein W Jr: Smoking and cervical cancer—Current status: a review. *Am J Epidemiol* 131:945-957, 1990.
- Ziegler RG, Brinton LA, Hamman RF, et al.: Diet and the risk of invasive cervical cancer among white women in the United States. *Am J Epidemiol* 132:432-445, 1990.

The uterus is a pear-shaped organ that lies in the abdomen between the bladder and the rectum. It consists of the cervix—the opening of the uterus into the vagina—and the corpus, sometimes called the body or womb. The corpus is composed of two layers of tissue. The spongy inside layer—the endometrium—proliferates between menses and is shed during menstruation if fertilization has not occurred. The outside layer, or myometrium, is a muscle capable of expanding during pregnancy to accommodate a growing fetus. Female sex hormones, including estrogen, prepare the uterus for pregnancy. Because most uterine cancers originate in the endometrium, cancers of this site can be assumed to be endometrial in origin unless specifically designated otherwise.

Uterine Corpus (Endometrium)

Louise A. Brinton, Ph.D.*

Cancer of the uterine corpus or endometrium is the third most common cancer among U.S. women and accounts for about 9 percent of their cancers. Fortunately, this disease causes a limited number of deaths, as reflected in the 83 percent five-year relative survival rate (Ries et al., 1994). Endometrial cancer is rare before the age of 45, but the risk rises sharply among women in their late 40s to mid 60s. Endometrial cancer rates are highest in North America and northern Europe; intermediate in Israel, southern Europe and Latin America; and low in Asia and Africa. In the United States, the age-adjusted incidence rates for whites are nearly twice as high as those for blacks; the reason for this discrepancy is unknown. Within the last several decades in the United States, there has been a dramatic change in the incidence pattern for endometrial cancer, characterized by a marked increase that peaked about 1975 and subsequently declined (Weiss et al., 1976). Considerable evidence has linked this rise and fall with the widespread use of estrogen replacement therapy in the late 1960s and early 1970s, followed by a dramatic reduction in such usage in the late 1970s.

Endometrial cancer and breast cancer share some of the same risk factors (Elwood et al., 1977; Hulka et al., 1980). Factors predisposing to both diseases include high socioeconomic status, never having given birth or having few children, early age at menarche, and late age at menopause. In contrast to breast cancer, late age at first birth has not been found to be a risk factor for endometrial cancer.

Multiple births have been linked to a decreased risk of endometrial cancer, with women who have had four or more children having only one-third the risk of women who have never had children. Women who have never had children, particularly those with a history of infertility, are at greatest risk. Studies of women with Stein-Leventhal syndrome, a rare condition characterized by multiple ovarian cysts, excessive estrogen production, and infertility, have been noted to be at particularly high risk for this cancer. Obesity, which is accompanied by increased levels of endogenous estrogens, has long been recognized as a risk factor for endometrial

* From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Uterine Corpus (Endometrium)

cancer, with very heavy women having disproportionately high risks (Swanson et al., 1993). Certain diseases that occur more commonly among overweight women, such as diabetes, high blood pressure, and gallbladder disease, have been linked with the occurrence of endometrial cancer, but it is unlikely that these conditions have independent effects on risk.

Despite extensive evidence linking obesity to the occurrence of endometrial cancer, few studies have investigated the potential role of dietary factors. There is some evidence of increases in risk with higher intakes of dietary fat (Potischman et al., 1993).

Most risk factors for endometrial cancer have been linked with hormonal imbalances, especially excess estrogen production. It is not surprising, therefore, that increased risk has been found among users of estrogen replacement therapy (Brinton et al., 1993; Hulka et al., 1980; Shapiro et al., 1985). Postmenopausal women who use estrogens have an estimated five- to ten-fold increased risk compared with nonusers, with risk increasing even further when use extends over many years or when high dose drugs are used. In most studies, risk appears to decrease rapidly with discontinuation of the estrogens (Hulka et al., 1980), although several studies suggest that elevated risk may continue for some time (Shapiro et al., 1985). To combat the adverse effects of estrogens on endometrial tissue, it has become commonplace for estrogens to be given in combination with a progestogen. Whether the combined therapy entirely eliminates the excess risk associated with estrogens alone has yet to be resolved (Brinton et al., 1993).

In contrast to menopausal estrogens, oral contraceptives containing both an estrogen and a progestin have been linked with lowered risks of endometrial cancer (Cancer and Steroid Hormone Study, 1987; Henderson et al., 1983; Weiss and Savvetz, 1980). However, an elevated risk was found in users of the sequential oral contraceptives, which included a regimen of a strong unopposed estrogen followed by limited exposure to a relatively weak progestin. These products are no longer marketed. Users of combination oral contraceptives have been found to have approximately half the risk of endometrial cancer compared to nonusers, and the longer the usage, the greater the apparent protection. In several studies, the protective effect of the pill appears most pronounced among high-risk childless women (Cancer and Steroid Hormone Study, 1987; Henderson et al., 1983).

REFERENCES

- Brinton LA, Hoover RN (the Endometrial Cancer Collaborative Group): Estrogen replacement therapy and endometrial cancer risk: Unresolved issues. *Obstet Gynecol* 81:265-271, 1993.
- Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. *JAMA* 257:796-800, 1987.
- Elwood JM, Cole P, Rothman KJ, et al.: Epidemiology of endometrial cancer. *J Natl Cancer Inst* 59:1055-1060, 1977.
- Henderson BE, Casagrande JT, Pike MC, et al.: The epidemiology of endometrial cancer in young women. *Br J Cancer* 47:749-756, 1983.
- Hulka BS, Fowler WC, Kaufman DG, et al.: Estrogen and endometrial cancer: Cases and two control groups from North Carolina. *Am J Obstet Gynecol* 137:92-101, 1980.
- Potischman N, Swanson CA, Brinton LA, et al.: Dietary associations in a case-control study of endometrial cancer. *Cancer Causes Control* 4:239-250, 1993.
- Ries LAG, Miller BA, Hankey BF, et al.: SEER Cancer Statistics Review, 1973-1991: Tables and Graphs, National Cancer Institute. NIH Publ. No. 94-2789, Bethesda, MD, 1994.
- Shapiro S, Kelly JP, Rosenberg L, et al.: Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. *N Engl J Med* 313:969-972, 1985.
- Swanson CA, Potischman N, Wilbanks GD, et al.: Relation of endometrial cancer risk to past and contemporary body size and body fat distribution. *Cancer Epidemiol Biomarker Prev* 2:321-327, 1993.
- Weiss NS and Sayvetz TA: Incidence of endometrial cancer in relation to the use of oral contraceptives. *N Engl J Med* 302:551-554, 1980.
- Weiss NS, Szkely DR and Austin DF: Increasing incidence of endometrial cancer in the United States. *N Engl J Med* 294:1259-1262, 1976.

